III. How Should Results of an Epidemiologic Study Be Interpreted?

Epidemiologists are ultimately interested in whether a causal relationship exists between an agent and a disease. However, the first question an epidemiologist addresses is whether an association exists between exposure to the agent and disease. An association between exposure to an agent and disease exists when they occur together more frequently than one would expect by chance.[42] Although a causal relationship is one possible explanation for an observed association between an exposure and a disease, an association does not necessarily mean that there is a cause–effect relationship. Interpreting the meaning of an observed association is discussed below.

This section begins by describing the ways of expressing the existence and strength of an association between exposure and disease. It reviews ways in which an incorrect result can be produced because of the sampling methods used in all observational epidemiologic studies and then examines statistical methods for evaluating whether an association is real or due to sampling error.

The strength of an association between exposure and disease can be stated as a relative risk, an odds ratio, or an attributable risk (often abbreviated as "RR," "OR," and "AR," respectively). Each of these measurements of association examines the degree to which the risk of disease increases when individuals are exposed to an agent.

A. Relative Risk

A commonly used approach for expressing the association between an agent and disease is relative risk (RR). It is defined as the ratio of the incidence rate (often referred to as incidence) of disease in exposed individuals to the incidence rate in unexposed individuals:

$$\text{Relative Risk (RR)} = \frac{\text{Incidence rate in the exposed}}{\text{Incidence rate in the unexposed}}$$

The incidence rate of disease reflects the number of cases of disease that develop during a specified period of time divided by the number of persons in the cohort under study.[43] Thus, the incidence rate expresses the risk that a

42. A negative association implies that the agent has a protective or curative effect. Because the concern in toxic substances litigation is whether an agent caused disease, this reference guide focuses on positive associations.

43. Epidemiologists also use the concept of prevalence, which measures the existence of disease in a population at a given point in time, regardless of when the disease developed. Prevalence is expressed as the proportion of the population with the disease at the chosen time. *See* Gordis, *supra* note 26, at 32–34.

member of the population will develop the disease within a specified period of time.

For example, a researcher studies 100 individuals who are exposed to an agent and 200 who are not exposed. After one year, 40 of the exposed individuals are diagnosed as having a disease, and 20 of the unexposed individuals also are diagnosed as having the disease. The relative risk of contracting the disease is calculated as follows:

- The incidence rate of disease in the exposed individuals is 40 cases per year per 100 persons (40/100), or 0.4.
- The incidence rate of disease in the unexposed individuals is 20 cases per year per 200 persons (20/200), or 0.1.
- The relative risk is calculated as the incidence rate in the exposed group (0.4) divided by the incidence rate in the unexposed group (0.1), or 4.0.

A relative risk of 4.0 indicates that the risk of disease in the exposed group is four times as high as the risk of disease in the unexposed group.[44]

In general, the relative risk can be interpreted as follows:

- If the relative risk equals 1.0, the risk in exposed individuals is the same as the risk in unexposed individuals. There is no association between exposure to the agent and disease.
- If the relative risk is greater than 1.0, the risk in exposed individuals is greater than the risk in unexposed individuals. There is a positive association between exposure to the agent and the disease, which could be causal.
- If the relative risk is less than 1.0, the risk in exposed individuals is less than the risk in unexposed individuals. There is a negative association, which could reflect a protective or curative effect of the agent on risk of disease. For example, immunizations lower the risk of disease. The results suggest that immunization is associated with a decrease in disease and may have a protective effect on the risk of disease.

Although relative risk is a straightforward concept, care must be taken in interpreting it. Researchers should scrutinize their results for error. Error in the design of a study could yield an incorrect relative risk. Sources of bias and confounding should be examined.[45] Whenever an association is uncovered, further analysis should be conducted to determine if the association is real or due to an error or bias. Similarly, a study that does not find an association between an agent and disease may be erroneous because of bias or random error.

44. *See* DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 947 (3d Cir. 1990); Gaul v. United States, 582 F. Supp. 1122, 1125 n.9 (D. Del. 1984).

45. *See infra* § IV.B–C.

are several meta-analyses of a given relationship, why do the results of different meta-analyses often disagree? Another consideration is that often the differences among the individual studies included in a meta-analysis and the reasons for the differences are important in themselves and need to be understood; however, they may be masked in a meta-analysis. A final problem with meta-analyses is that they generate a single estimate of risk and may lead to a false sense of security regarding the certainty of the estimate. People often tend to have an inordinate belief in the validity of the findings when a single number is attached to them, and many of the difficulties that may arise in conducting a meta-analysis, especially of observational studies like epidemiologic ones, may consequently be overlooked.[127]

VII. What Role Does Epidemiology Play in Proving Specific Causation?

Epidemiology is concerned with the incidence of disease in populations and does not address the question of the cause of an individual's disease.[128] This question, sometimes referred to as specific causation, is beyond the domain of the science of epidemiology. Epidemiology has its limits at the point where an

127. Much has been written about meta-analysis recently, and some experts consider the problems of meta-analysis to outweigh the benefits at the present time. For example, Bailar has written the following:

> [P]roblems have been so frequent and so deep, and overstatements of the strength of conclusions so extreme, that one might well conclude there is something seriously and fundamentally wrong with the method. For the present . . . I still prefer the thoughtful, old-fashioned review of the literature by a knowledgeable expert who explains and defends the judgments that are presented. We have not yet reached a stage where these judgments can be passed on, even in part, to a formalized process such as meta-analysis.

John C. Bailar III, *Assessing Assessments*, 277 Science 528, 529 (1997) (reviewing Morton Hunt, How Science Takes Stock (1997)); *see also Point/Counterpoint: Meta-analysis of Observational Studies*, 140 Am. J. Epidemiology 770 (1994).

128. *See* DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 945 & n.6 (3d Cir. 1990) ("Epidemiological studies do not provide direct evidence that a particular plaintiff was injured by exposure to a substance."); Smith v. Ortho Pharm. Corp., 770 F. Supp. 1561, 1577 (N.D. Ga. 1991); Grassis v. Johns-Manville Corp., 591 A.2d 671, 675 (N.J. Super. Ct. App. Div. 1991); Michael Dore, *A Commentary on the Use of Epidemiological Evidence in Demonstrating Cause-in-Fact*, 7 Harv. Envtl. L. Rev. 429, 436 (1983).

There are some diseases that do not occur without exposure to a given toxic agent. This is the same as saying that the toxic agent is a necessary cause for the disease, and the disease is sometimes referred to as a signature disease (also, the agent is pathognomonic), because the existence of the disease necessarily implies the causal role of the agent. *See* Kenneth S. Abraham & Richard A. Merrill, *Scientific Uncertainty in the Courts*, Issues Sci. & Tech., Winter 1986, at 93, 101. Asbestosis is a signature disease for asbestos, and adenocarcinoma (in young adult women) is a signature disease for in utero DES exposure. *See In re* "Agent Orange" Prod. Liab. Litig., 597 F. Supp. 740, 834 (E.D.N.Y. 1984) (Agent Orange allegedly caused a wide variety of diseases in Vietnam veterans and their offspring), *aff'd*, 818 F.2d 145 (2d Cir. 1987), *cert. denied*, 484 U.S. 1004 (1988).

inference is made that the relationship between an agent and a disease is causal (general causation) and where the magnitude of excess risk attributed to the agent has been determined; that is, epidemiology addresses whether an agent can cause a disease, not whether an agent did cause a specific plaintiff's disease.[129]

Nevertheless, the specific causation issue is a necessary legal element in a toxic substance case. The plaintiff must establish not only that the defendant's agent is capable of causing disease but also that it did cause the plaintiff's disease. Thus, a number of courts have confronted the legal question of what is acceptable proof of specific causation and the role that epidemiologic evidence plays in answering that question.[130] This question is not a question that is addressed by epidemiology.[131] Rather, it is a legal question a number of courts have grappled with. An explanation of how these courts have resolved this question follows. The remainder of this section should be understood as an explanation of judicial opinions, not as epidemiology.

Before proceeding, one last caveat is in order. This section assumes that epidemiologic evidence has been used as proof of causation for a given plaintiff. The discussion does not address whether a plaintiff must use epidemiologic evidence to prove causation.[132]

Two legal issues arise with regard to the role of epidemiology in proving individual causation: admissibility and sufficiency of evidence to meet the burden of production. The first issue tends to receive less attention by the courts but nevertheless deserves mention. An epidemiologic study that is sufficiently rigorous to justify a conclusion that it is scientifically valid should be admissible,[133] as it tends to make an issue in dispute more or less likely.[134]

129. *Cf.* *"Agent Orange,"* 597 F. Supp. at 780.

130. In many instances causation can be established without epidemiologic evidence. When the mechanism of causation is well understood, the causal relationship is well established, or the timing between cause and effect is close, scientific evidence of causation may not be required. This is frequently the situation when the plaintiff suffers traumatic injury rather than disease. This section addresses only those situations in which causation is not evident and scientific evidence is required.

131. Nevertheless, an epidemiologist may be helpful to the fact finder in answering this question. Some courts have permitted epidemiologists (or those who use epidemiologic methods) to testify about specific causation. *See* Ambrosini v. Labarraque, 101 F.3d 129, 137–41 (D.C. Cir. 1996), *cert. dismissed*, 520 U.S. 1205 (1997); Zuchowicz v. United States, 870 F. Supp. 15 (D. Conn. 1994); Landrigan v. Celotex Corp., 605 A.2d 1079, 1088–89 (N.J. 1992). In general, courts seem more concerned with the basis of an expert's opinion than with whether the expert is an epidemiologist or clinical physician. *See* Porter v. Whitehall, 9 F.3d 607, 614 (7th Cir. 1992) ("curb side" opinion from clinician not admissible); Wade-Greaux v. Whitehall Labs., 874 F. Supp. 1441, 1469–72 (D.V.I.) (clinician's multiple bases for opinion inadequate to support causation opinion), *aff'd*, 46 F.3d 1120 (3d Cir. 1994); *Landrigan*, 605 A.2d at 1083–89 (permitting both clinicians and epidemiologists to testify to specific causation provided the methodology used is sound).

132. *See* Green, *supra* note 39, at 672–73; 2 Modern Scientific Evidence, *supra* note 2, § 28-1.3.2 to -1.3.3, at 306–11.

133. *See DeLuca*, 911 F.2d at 958; *cf.* Kehm v. Procter & Gamble Co., 580 F. Supp. 890, 902 (N.D. Iowa 1982) ("These [epidemiologic] studies were highly probative on the issue of causation—they all

Far more courts have confronted the role that epidemiology plays with regard to the sufficiency of the evidence and the burden of production. The civil burden of proof is described most often as requiring the fact finder to "believe that what is sought to be proved . . . is more likely true than not true."[135] The relative risk from epidemiologic studies can be adapted to this 50% plus standard to yield a probability or likelihood that an agent caused an individual's disease.[136] An important caveat is necessary, however. The discussion below speaks in terms of the magnitude of the relative risk or association found in a study. However, before an association or relative risk is used to make a statement about the probability of individual causation, the inferential judgment, described in section V, that the association is truly causal rather than spurious is required: "[A]n agent cannot be considered to cause the illness of a specific person unless

concluded that an association between tampon use and menstrually related TSS [toxic shock syndrome] cases exists."), *aff'd sub nom.* Kehm v. Procter & Gamble Mfg. Co., 724 F.2d 613 (8th Cir. 1984).

Hearsay concerns may limit the independent admissibility of the study (*see supra* note 3), but the study could be relied on by an expert in forming an opinion and may be admissible pursuant to Fed. R. Evid. 703 as part of the underlying facts or data relied on by the expert.

In *Ellis v. International Playtex, Inc.*, 745 F.2d 292, 303 (4th Cir. 1984), the court concluded that certain epidemiologic studies were admissible despite criticism of the methodology used in the studies. The court held that the claims of bias went to the studies' weight rather than their admissibility. *Cf.* Christophersen v. Allied-Signal Corp., 939 F.2d 1106, 1109 (5th Cir. 1991) ("As a general rule, questions relating to the bases and sources of an expert's opinion affect the weight to be assigned that opinion rather than its admissibility . . . . "), *cert. denied*, 503 U.S. 912 (1992).

134. Even if evidence is relevant, it may be excluded if its probative value is substantially outweighed by prejudice, confusion, or inefficiency. Fed. R. Evid. 403. However, exclusion of an otherwise relevant epidemiologic study on Rule 403 grounds is unlikely.

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 591 (1993), the Court invoked the concept of "fit," which addresses the relationship of an expert's scientific opinion to the facts of the case and the issues in dispute. In a toxic substance case in which cause in fact is disputed, an epidemiologic study of the same agent to which the plaintiff was exposed that examined the association with the same disease from which the plaintiff suffers would undoubtedly have sufficient "fit" to be a part of the basis of an expert's opinion. The Court's concept of "fit," borrowed from *United States v. Downing*, 753 F.2d 1224, 1242 (3d Cir. 1985), appears equivalent to the more familiar evidentiary concept of probative value, albeit one requiring assessment of the scientific reasoning the expert used in drawing inferences from methodology or data to opinion.

135. 2 Edward J. Devitt & Charles B. Blackmar, Federal Jury Practice and Instruction § 71.13 (3d ed. 1977); *see also* United States v. Fatico, 458 F. Supp. 388, 403 (E.D.N.Y. 1978) ("Quantified, the preponderance standard would be 50%+ probable."), *aff'd*, 603 F.2d 1053 (2d Cir. 1979), *cert. denied*, 444 U.S. 1073 (1980).

136. An adherent of the frequentist school of statistics would resist this adaptation, which may explain why so many epidemiologists and toxicologists also resist it. To take the step identified in the text of using an epidemiologic study outcome to determine the probability of specific causation requires a shift from a frequentist approach, which involves sampling or frequency data from an empirical test, to a subjective probability about a discrete event. Thus, a frequentist might assert, after conducting a sampling test, that 60% of the balls in an opaque container are blue. The same frequentist would resist the statement, "The probability that a single ball removed from the box and hidden behind a screen is blue is 60%." The ball is either blue or not, and no frequentist data would permit the latter statement. "[T]here is no logically rigorous definition of what a statement of probability means with reference to an individual instance . . . ." Lee Loevinger, *On Logic and Sociology*, 32 Jurimetrics J. 527, 530 (1992); *see*

it is recognized as a cause of that disease in general."[137] The following discussion should be read with this caveat in mind.[138]

The threshold for concluding that an agent was more likely than not the cause of an individual's disease is a relative risk greater than 2.0. Recall that a relative risk of 1.0 means that the agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other background causes. Thus, a relative risk of 2.0 (with certain qualifications noted below) implies a 50% likelihood that an exposed individual's disease was caused by the agent. A relative risk greater than 2.0 would permit an inference that an individual plaintiff's disease was more likely than not caused by the implicated agent.[139] A substantial number of courts in a variety of toxic substances cases have accepted this reasoning.[140]

also Steve Gold, Note, *Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion and Statistical Evidence*, 96 Yale L.J. 376, 382–92 (1986). Subjective probabilities about discrete events are the product of adherents to Bayes Theorem. *See* Kaye, *supra* note 67, at 54–62; David H. Kaye & David A. Freedman, Reference Guide on Statistics § IV.D, in this manual.

137. Cole, *supra* note 53, at 10284.

138. We emphasize this caveat, both because it is not intuitive and because some courts have failed to appreciate the difference between an association and a causal relationship. *See, e.g.*, Forsyth v. Eli Lilly & Co., Civ. No. 95-00185 ACK, 1998 U.S. Dist. LEXIS 541, at *26–*31 (D. Haw. Jan. 5, 1998). *But see* Berry v. CSX Transp., Inc., 709 So. 2d 552, 568 (Fla. Dist. Ct. App. 1998) ("From epidemiological studies demonstrating an association, an epidemiologist may or may not infer that a causal relationship exists.").

139. *See* Davies v. Datapoint Corp., No. 94-56-P-DMC, 1995 U.S. Dist. LEXIS 21739, at *32–*35 (D. Me. Oct. 31, 1995) (holding that epidemiologist could testify about specific causation, basing such testimony on the probabilities derived from epidemiologic evidence).

140. *See* DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 958–59 (3d Cir. 1990) (Bendectin allegedly caused limb reduction birth defects); *In re* Joint E. & S. Dist. Asbestos Litig., 964 F.2d 92 (2d Cir. 1992) (relative risk less than 2.0 may still be sufficient to prove causation); Daubert v. Merrell Dow Pharms., Inc., 43 F.3d 1311, 1320 (9th Cir.) (requiring that plaintiff demonstrate a relative risk of 2), *cert. denied*, 516 U.S. 869 (1995); Pick v. American Med. Sys., Inc., 958 F. Supp. 1151, 1160 (E.D. La. 1997) (recognizing that a relative risk of 2 implies a 50% probability of specific causation, but recognizing that a study with a lower relative risk is admissible, although ultimately it may be insufficient to support a verdict on causation); Sanderson v. International Flavors & Fragrances, Inc., 950 F. Supp. 981, 1000 (C.D. Cal. 1996) (acknowledging a relative risk of 2 as a threshold for plaintiff to prove specific causation); Manko v. United States, 636 F. Supp. 1419, 1434 (W.D. Mo. 1986) (swine flu vaccine allegedly caused Guillain-Barré syndrome), *aff'd in part*, 830 F.2d 831 (8th Cir. 1987); Marder v. G.D. Searle & Co., 630 F. Supp. 1087, 1092 (D. Md. 1986) (pelvic inflammatory disease allegedly caused by Copper 7 IUD), *aff'd without op. sub nom.* Wheelahan v. G.D. Searle & Co., 814 F.2d 655 (4th Cir. 1987); *In re* "Agent Orange" Prod. Liab. Litig., 597 F. Supp. 740, 835–37 (E.D.N.Y. 1984) (Agent Orange allegedly caused a wide variety of diseases in Vietnam veterans and their offspring), *aff'd*, 818 F.2d 145 (2d Cir. 1987), *cert. denied*, 484 U.S. 1004 (1988); Cook v. United States, 545 F. Supp. 306, 308 (N.D. Cal. 1982) (swine flu vaccine allegedly caused Guillain-Barré syndrome); Landrigan v. Celotex Corp., 605 A.2d 1079, 1087 (N.J. 1992) (relative risk greater than 2.0 "support[s] an inference that the exposure was the probable cause of the disease in a specific member of the exposed population"); Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 718 (Tex. 1997) ("The use of scientifically reliable epidemiological studies and the requirement of more than a doubling of the risk strikes a balance between the needs of our legal system and the limits of science."). *But cf. In re* Fibreboard Corp., 893 F.2d 706, 711–12 (5th Cir. 1990) (The court disapproved a trial in which several representative

An alternative, yet similar, means to address probabilities in individual cases is use of the attributable risk parameter.[141] The attributable risk is a measurement of the excess risk that can be attributed to an agent, above and beyond the background risk that is due to other causes.[142] When the attributable risk exceeds 50% (equivalent to a relative risk greater than 2.0), this logically might lead one to believe that the agent was more likely than not the cause of the plaintiff's disease.

The discussion above contains a number of assumptions: that the study was unbiased, sampling error and confounding were judged unlikely or minimal, the causal factors discussed in section V point toward causation, and the relative risk found in the study is a reasonably accurate measure of the extent of disease caused by the agent. It also assumes that the plaintiff in a given case is comparable to the subjects who made up the exposed cohort in the epidemiologic study and that there are no interactions with other causal agents.[143]

Evidence in a given case may challenge one or more of those assumptions. Bias in a study may suggest that the outcome found is inaccurate and should be estimated to be higher or lower than the actual result. A plaintiff may have been exposed to a dose of the agent in question that is greater or lower than that to which those in the study were exposed.[144] A plaintiff may have individual factors, such as higher age than those in the study, that make it less likely that

cases would be tried and the results extrapolated to a class of some 3,000 asbestos victims, without consideration of any evidence about the individual victims. The court remarked that under Texas law, general causation, which ignores any proof particularistic to the individual plaintiff, could not be substituted for cause in fact.).

141. *See supra* § III.C.

142. Because cohort epidemiologic studies compare the incidences (rates) of disease, measures like the relative risk and attributable risk are dependent on the time period during which disease is measured in the study groups. Exposure to the agent may either accelerate the onset of the disease in a subject who would have contracted the disease at some later time—all wrongful death cases entail acceleration of death—or be the cause of disease that otherwise would never have occurred in the subject. This creates some uncertainty (when pathological information does not permit determining which of the foregoing alternatives is the case) and ambiguity about the proper calculation of the attributable risk, that is, whether both alternatives should be included in the excess risk or just the latter. *See* Sander Greenland & James M. Robins, *Conceptual Problems in the Definition and Interpretation of Attributable Fractions*, 128 Am. J. Epidemiology 1185 (1988). If information were available, the legal issue with regard to acceleration would be the characterization of the harm and the appropriate amount of damages when a defendant's tortious conduct accelerates development of the disease. *See* Restatement (Second) of Torts § 924 cmt. e (1977); Keeton et al., *supra* note 107, § 52, at 353–54; Robert J. Peaslee, *Multiple Causation and Damages*, 47 Harv. L. Rev. 1127 (1934).

143. *See* Greenland & Robins, *supra* note 142, at 1193.

144. *See supra* § V.C; *see also* Ferebee v. Chevron Chem. Co., 736 F.2d 1529, 1536 (D.C. Cir.) ("The dose–response relationship at low levels of exposure for admittedly toxic chemicals like paraquat is one of the most sharply contested questions currently being debated in the medical community."), *cert. denied*, 469 U.S. 1062 (1984); *In re* Joint E. & S. Dist. Asbestos Litig., 774 F. Supp. 113, 115 (S.D.N.Y. 1991) (discussing different relative risks associated with different doses), *rev'd on other grounds*, 964 F.2d 92 (2d Cir. 1992).

exposure to the agent caused the plaintiff's disease. Similarly, an individual plaintiff may be able to rule out other known (background) causes of the disease, such as genetics, that increase the likelihood that the agent was responsible for that plaintiff's disease. Pathological-mechanism evidence may be available for the plaintiff that is relevant to the cause of the plaintiff's disease.[145] Before any causal relative risk from an epidemiologic study can be used to estimate the probability that the agent in question caused an individual plaintiff's disease, consideration of these (and similar) factors is required.[146]

Having additional evidence that bears on individual causation has led a few courts to conclude that a plaintiff may satisfy his or her burden of production even if a relative risk less than 2.0 emerges from the epidemiologic evidence.[147] For example, genetics might be known to be responsible for 50% of the incidence of a disease independent of exposure to the agent.[148] If genetics can be ruled out in an individual's case, then a relative risk greater than 1.5 might be sufficient to support an inference that the agent was more likely than not responsible for the plaintiff's disease.[149]

145. *See* Tobin v. Astra Pharm. Prods., Inc., 993 F.2d 528 (6th Cir.) (plaintiff's expert relied predominantly on pathogenic evidence), *cert. denied*, 510 U.S. 914 (1993).

146. *See* Merrell Dow Pharms., Inc. v. Havner, 953 S.W.2d 706, 720 (Tex. 1997); Mary Carter Andrues, Note, *Proof of Cancer Causation in Toxic Waste Litigation*, 61 S. Cal. L. Rev. 2075, 2100–04 (1988). An example of a judge sitting as fact finder and considering individual factors for a number of plaintiffs in deciding cause in fact is contained in *Allen v. United States*, 588 F. Supp. 247, 429–43 (D. Utah 1984), *rev'd on other grounds*, 816 F.2d 1417 (10th Cir. 1987), *cert. denied*, 484 U.S. 1004 (1988); *see also* Manko v. United States, 636 F. Supp. 1419, 1437 (W.D. Mo. 1986), *aff'd*, 830 F.2d 831 (8th Cir. 1987).

147. *See, e.g.*, Grassis v. Johns-Manville Corp., 591 A.2d 671, 675 (N.J. Super. Ct. App. Div. 1991): "The physician or other qualified expert may view the epidemiological studies and factor out other known risk factors such as family history, diet, alcohol consumption, smoking . . . or other factors which might enhance the remaining risks, even though the risk in the study fell short of the 2.0 correlation." *See also In re* Joint E. & S. Dist. Asbestos Litig., 52 F.3d 1124 (2d Cir. 1995) (holding that plaintiff could provide sufficient evidence of causation without proving a relative risk greater than 2); *In re* Joint E. & S. Dist. Asbestos Litig., 964 F.2d 92, 97 (2d Cir. 1992), *rev'g* 758 F. Supp. 199, 202–03 (S.D.N.Y. 1991) (requiring relative risk in excess of 2.0 for plaintiff to meet burden of production); Jones v. Owens-Corning Fiberglas Corp., 672 A.2d 230 (N.J. Super. Ct. App. Div. 1996).

148. *See In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717, 758–59 (3d Cir. 1994) (discussing the technique of differential diagnosis to rule out other known causes of a disease for a specific individual).

149. The use of probabilities in excess of .50 to support a verdict results in an all-or-nothing approach to damages that some commentators have criticized. The criticism reflects the fact that defendants responsible for toxic agents with a relative risk just above 2.0 may be required to pay damages not only for the disease that their agents caused, but also for all instances of the disease. Similarly, those defendants whose agents increase the risk of disease by less than a doubling may not be required to pay damages for any of the disease that their agents caused. *See, e.g.*, 2 American Law Inst., Reporter's Study on Enterprise Responsibility for Personal Injury: Approaches to Legal and Institutional Change 369–75 (1991). To date, courts have not adopted a rule that would apportion damages based on the probability of cause in fact in toxic substances cases.

until it reaches the target organ is often called physiologically based pharmacokinetics.[27]

Extrapolation from studies in nonmammalian species to humans is much more difficult and can only be done if there is sufficient information on similarities in absorption, distribution, metabolism, and excretion; quantitative determinations of human toxicity based on in vitro studies usually are not considered appropriate. As discussed in section I.F, in vitro or animal data for elucidating mechanisms of toxicity are more persuasive when positive human epidemiological data also exist.[28]

E. Safety and Risk Assessment

Toxicological expert opinion also relies on formal safety and risk assessments. Safety assessment is the area of toxicology relating to the testing of chemicals and drugs for toxicity. It is a relatively formal approach in which the potential for toxicity of a chemical is tested in vivo or in vitro using standardized techniques. The protocols for such studies usually are developed through scientific consensus and are subject to oversight by governmental regulators or other watchdog groups.

After a number of bad experiences, including outright fraud, government agencies have imposed codes on laboratories involved in safety assessment, including industrial, contract, and in-house laboratories.[29] Known as Good Laboratory Practice (GLP), these codes govern many aspects of laboratory standards,

bone marrow in all species, including humans. Robert Snyder et al., *The Toxicology of Benzene*, 100 Envtl. Health Persp. 293 (1993). The exact metabolites responsible for this bone-marrow toxicity are the subject of much interest but remain unknown. Mice are more susceptible to benzene than are rats. If researchers could determine the differences between mice and rats in their metabolism of benzene, they would have a useful clue as to which portion of the metabolic scheme is responsible for benzene toxicity to the bone marrow. *See, e.g.*, Karl K. Rozman & Curtis D. Klaassen, *Absorption, Distribution, and Excretion of Toxicants*, *in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 91; Andrew Parkinson, *Biotransformation of Xenobiotics*, *in* Casarett and Doull's Toxicology: The Basic Science of Poisons, *supra* note 1, at 113.

27. For an analysis of methods used to extrapolate from animal toxicity data to human health effects, see, e.g., Robert E. Menzer, *Selection of Animal Models for Data Interpretation*, *in* Toxic Substances and Human Risk: Principles of Data Interpretation, *supra* note 15, at 133; Thomas J. Slaga, *Interspecies Comparisons of Tissue DNA Damage, Repair, Fixation and Replication*, 77 Envtl. Health Persp. 73 (1988); Lorenzo Tomatis, *The Predictive Value of Rodent Carcinogenicity Tests in the Evaluation of Human Risks*, 19 Ann. Rev. Pharmacol. & Toxicol. 511 (1979); Willard J. Visek, *Issues and Current Applications of Interspecies Extrapolation of Carcinogenic Potency as a Component of Risk Assessment*, 77 Envtl. Health Persp. 49 (1988); Gary P. Carlson, *Factors Modifying Toxicity*, *in* Toxic Substances and Human Risk: Principles of Data Interpretation, *supra* note 15, at 47; Michael D. Hogan & David G. Hoel, *Extrapolation to Man*, *in* Principles and Methods of Toxicology, *supra* note 14, at 879; James P. Leape, *Quantitative Risk Assessment in Regulation of Environmental Carcinogens*, 4 Harv. Envtl. L. Rev. 86 (1980).

28. *See, e.g.*, Goewey v. United States, 886 F. Supp. 1268, 1280–81 (D.S.C. 1995) (extrapolation of neurotoxic effects from chickens to humans unwarranted without human confirmation).

29. A dramatic case of fraud involving a toxicology laboratory that performed tests to assess the

including such details as the number of animals per cage, dose and chemical verification, and the handling of tissue specimens. GLP practices are remarkably similar across agencies, but the tests called for differ depending on mission. For example, there are major differences between the FDA's and the EPA's required procedures for testing drugs and environmental chemicals.[30] The FDA requires and specifies both efficacy and safety testing of drugs in humans and animals. Carefully controlled clinical trials using doses within the expected therapeutic range are required for premarket testing of drugs because exposures to prescription drugs are carefully controlled and should not exceed specified ranges or uses. However, for environmental chemicals and agents, no premarket testing in humans is required by the EPA. Moreover, since exposures are less predictable, a wider range of doses usually is given in the animal tests.[31]

Since exposures to environmental chemicals may continue over the lifetime and affect both young and old, test designs called lifetime bioassays have been developed in which relatively high doses are given to experimental animals. Interpretation of results requires extrapolation from animals to humans, from high to low doses, and from short exposures to multiyear estimates. It must be emphasized that less than 1% of the 60,000–75,000 chemicals in commerce have been subjected to a full safety assessment, and there are significant toxicological data on only 10%–20%.

Risk assessment is an approach increasingly used by regulatory agencies to estimate and compare the risks of hazardous chemicals and to assign priority for avoiding their adverse effects.[32] The National Academy of Sciences defines four components of risk assessment: hazard identification, dose–response estimation, exposure assessment, and risk characterization.[33]

Although risk assessment is not an exact science, it should be viewed as a

safety of consumer products is described in *United States v. Keplinger*, 776 F.2d 678 (7th Cir. 1985), *cert. denied*, 476 U.S. 1183 (1986). Keplinger and the other defendants in this case were toxicologists who were convicted of falsifying data on product safety by underreporting animal morbidity and mortality and omitting negative data and conclusions from their reports.

30. *See, e.g.*, 40 C.F.R. §§ 160, 792 (1993); Lu, *supra* note 14, at 89.

31. It must be appreciated that the development of a new drug inherently requires searching for an agent that at useful doses has a biological effect (e.g., decreasing blood pressure), whereas those developing a new chemical for consumer use (e.g., a house paint) hope that at usual doses no biological effects will occur. There are other compounds, such as pesticides and antibacterial agents, for which a biological effect is desired, but it is intended that at usual doses humans will not be affected. These different expectations are part of the rationale for the differences in testing information available for assessing toxicological effects.

32. Committee on Risk Assessment Methodology, National Research Council, *supra* note 19, at 1.

33. *See generally* National Research Council, Risk Assessment in the Federal Government: Managing the Process (1983); Bernard D. Goldstein, *Risk Assessment/Risk Management Is a Three-Step Process: In Defense of EPA's Risk Assessment Guidelines*, 7 J. Am. C. Toxicol. 543 (1988); Bernard D. Goldstein, *Risk Assessment and the Interface Between Science and Law*, 14 Colum. J. Envtl. L. 343 (1989).

useful estimate on which policy making can be based. In recent years, codification of the methodology used to assess risk has increased confidence that the process can be reasonably free of bias; however, significant controversy remains, particularly when actual data are limited and generally conservative default assumptions are used.[34]

While risk assessment information about a chemical can be somewhat useful in a toxic tort case, at least in terms of setting reasonable boundaries as to the likelihood of causation, the impetus for the development of risk assessment has been the regulatory process, which has different goals.[35] Because of their use of appropriately prudent assumptions in areas of uncertainty and their use of default assumptions when there are limited data, risk assessments intentionally encompass the upper range of possible risks.

F. Toxicology and Epidemiology

Epidemiology is the study of the incidence and distribution of disease in human populations. Clearly, both epidemiology and toxicology have much to offer in elucidating the causal relationship between chemical exposure and disease.[36] These sciences often go hand in hand in assessments of the risks of chemical exposure, without artificial distinctions being drawn between them. However, although courts generally rule epidemiological expert opinion admissible, admissibility of toxicological expert opinion has been more controversial because of uncertain-

34. An example of conservative default assumptions can be found in Superfund risk assessment. The EPA has determined that Superfund sites should be cleaned up to reduce cancer risk from 1 in 10,000 to 1 in 1,000,000. A number of assumptions can go into this calculation, including conservative assumptions about intake, exposure frequency and duration, and cancer-potency factors for the chemicals at the site. *See, e.g.*, Robert H. Harris & David E. Burmaster, *Restoring Science to Superfund Risk Assessment*, 6 Toxics L. Rep. (BNA) 1318 (Mar. 25, 1992).

35. *See, e.g.*, Ellen Relkin, *Use of Governmental and Industrial Standards of Exposure and Toxicological Data in Toxic Tort Litigation, reprinted in* Proving Causation of Disease: Update 1996, at 199 (New Jersey Inst. for Continuing Legal Educ. 1996); Steven Shavell, *Liability for Harm Versus Regulation of Safety*, 13 J. Legal Stud. 357 (1984). Risk assessment has been heavily criticized on a number of grounds. The major argument of industry has been that it is overly conservative and thus greatly overstates the actual risk. The rationale for conservatism is in part the prudent public health approach of "above all, do no harm." The conservative approach is also used, especially in regard to cancer risk, because it is sometimes more feasible to extrapolate to a plausible upper boundary for a risk estimate than it is to estimate a point of maximum likelihood. For a sample of the debate over risk assessment, see Bruce N. Ames & Lois S. Gold, *Too Many Rodent Carcinogens: Mitogenesis Increases Mutagenesis*, 249 Science 970 (1990); Jean Marx, *Animal Carcinogen Testing Challenged*, 250 Science 743 (1990); Philip H. Abelson, *Incorporation of a New Science into Risk Assessment*, 250 Science 1497 (1990); Frederica P. Perera, *Letter to the Editor: Carcinogens and Human Health, Part 1*, 250 Science 1644 (1990); Bruce N. Ames & Lois S. Gold, *Response*, 250 Science 1645 (1990); David P. Rall, *Letter to the Editor: Carcinogens and Human Health, Part 2*, 251 Science 10 (1991); Bruce N. Ames & Lois S. Gold, *Response*, 251 Science 12 (1991); John C. Bailar III et al., *One-Hit Models of Carcinogenesis: Conservative or Not?*, 8 Risk Analysis 485 (1988).

36. *See* Michael D. Green et al., Reference Guide on Epidemiology § V, in this manual.

physicians in thinking through a differential diagnosis. For instance, heart attacks are very rare in 25-year-olds and relatively more common in 75-year-olds. In analyzing a patient with chest pain and borderline abnormal EKG changes, the physician is much more likely to suspect a heart attack as the cause of the pain in the 75-year-old, and admit the patient to a hospital, at least for monitoring.[109]

Diagnostic reasoning is usually more complex than the examples given because it is simultaneously based on multiple symptoms, signs, and test results (e.g., family history, physical exam). These findings are not all truly independent of one another, thus preventing straightforward addition of the probabilities as in a Bayesian model. This lack of independence limits the ability of physicians to make accurate calculations of the results of multiple simultaneous predictive values. However, physicians must routinely make such estimations, albeit often implicitly and without numerical quantification, as part of clinical care. Thus, physicians frequently rely on the principles of Bayesian reasoning when deciding on a diagnosis.[110] Doctors combine probabilities of disease (prevalence) with their knowledge of the frequency of signs and symptoms in a given disease and competing diseases to progressively modify and ultimately arrive at their view of the likelihood of the disease under consideration.

D. Causal Reasoning

During the diagnostic process, the physician employs causal reasoning to integrate the various clinical variables into an understanding of the cause-and-effect relationships among them, based on an understanding of how the various systems of the human body interact and react to external stressors. Causal reasoning allows the clinician to conceptualize the possible course of the patient's disease and predict the effects of treatment, and is important in evaluating the coherency of a diagnosis. For example, if the patient is experiencing chest pain on exertion and has a history of high blood cholesterol levels, the physician might posit a causal model that involves cholesterol plaque substantially obstructing coronary arteries, resulting in inadequate blood flow to the heart muscle during exercise causing chest pain. This model might then suggest that the physician first investigate the degree of occlusion in the coronary arteries, and second

109. The positive predictive value of a symptom of chest pain for a heart attack is very low in a 25-year-old because advanced atherosclerotic cardiovascular disease is rare in this age group and other causes of chest pain are more common. Similarly, interstitial fibrosis on a chest x-ray, whatever the x-ray's sensitivity and specificity for a true underlying finding of pathologic fibrosis, has a much higher predictive value for a diagnosis of asbestosis in a person known to come from an asbestos-exposed population than in someone with no known occupational exposure to asbestos.

110. *See* Kassirer & Kopelman, *supra* note 48, at 19–24; Steven N. Goodman, *Toward Evidence-Based Medical Statistics. 2: The Bayes Factor*, 130 Annals Internal Med. 1005, 1011 (1999).

consider measures such as smoking cessation, dietary modification, medications, and even angioplasty or surgery if the level of occlusion proves to be substantial and a likely explanation for the pain.

As the process of refinement of diagnostic hypotheses unfolds, the consideration of several causal models may be necessary, because consistency of the model with observed findings does not necessarily prove that a model is correct. In the example above, another model that would explain the findings is exposure to high levels of carbon monoxide from a faulty furnace at home, producing a blood carboxyhemoglobin level of 18% (the normal for a nonsmoker is less than 1%) and reducing the blood's oxygen-carrying capacity. In conjunction with only mild coronary artery obstruction by plaque, this exposure then leads to inadequate oxygen delivery to the heart muscle and chest pain. The model combines general causation models for coronary artery disease with information on the levels of carbon monoxide and coronary artery obstruction specific to this patient. Thus, the physician applies general medical knowledge about the relationship of various factors to symptoms and then refines the appropriate causal model in accordance with the specific patient's condition. Although carbon monoxide intoxication can cause chest pain that is due to inadequate oxygen delivery to the heart, it requires a blood carboxyhemoglobin level of at least 5% to 10%, and its impact is enhanced by the presence of underlying mechanical obstruction of the coronary arteries. Hence, the physician must usually consider and assess alternative and more specific causal models before accepting a particular model as the preferred explanation. Like the probabilistic reasoning described above, this kind of reasoning is rarely made explicit.

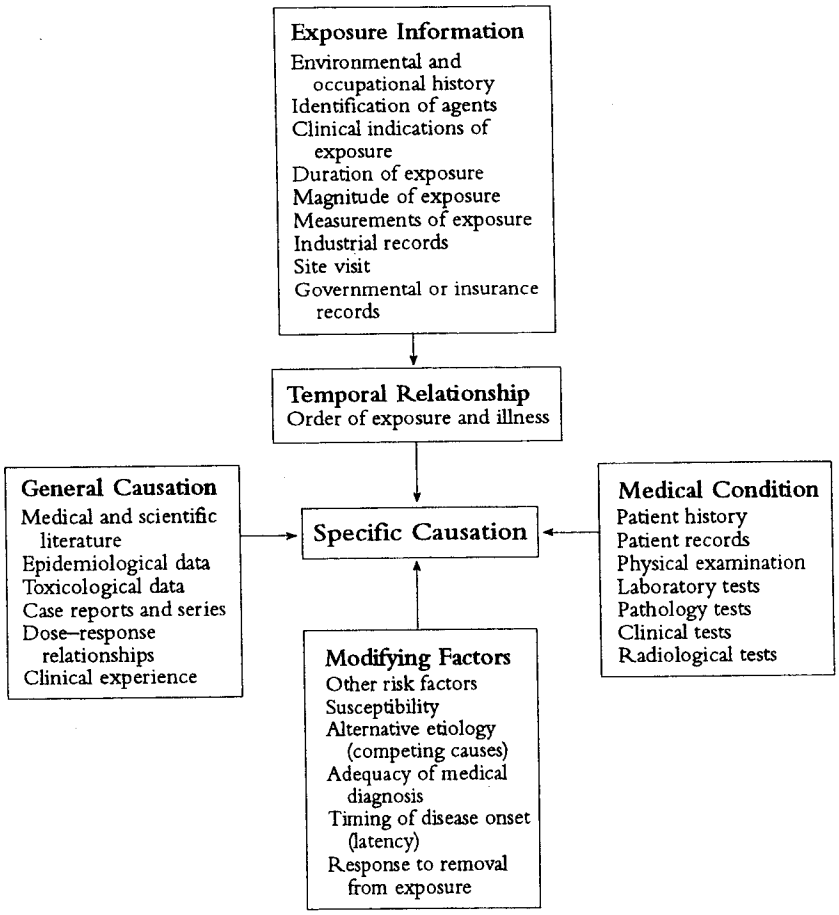
E. Evaluation of External Causation

For the physician, both causal and probabilistic reasoning are the basis for establishing external causation, which is the relationship between environmental factors (work, chemical exposures, lifestyle, medications) and illness, as well as for making the more common analysis of internal causation as discussed earlier in section IV.B. The physician may be asked to determine external causation by the patient or a third party, such as a lawyer, insurance company, or governmental agency. A key element of determining causation is gaining access to all information available about the patient's condition.

Figure 1 provides examples of the diverse types of information that may be available for review in determining external causation. In any given case, much of the listed information is normally not available.[111] Determining external causation also generally occurs in a stepwise fashion. In the first step the physician

111. For a somewhat different illustration of the interaction of such factors, see Cullen et al., *supra* note 19, at 230 fig.18-2.

Figure 1. Determining External Causation



must establish the characteristics of the medical condition. Second, he or she carefully defines the nature and amount of the environmental exposure. The third step is to demonstrate that the medical and scientific literature provides evidence that in some circumstances the exposure under consideration can cause the outcome under consideration. This step is synonymous with establishment of general causation. As part of this step, the clinician attempts to establish the relationship between dose and response, including whether thresholds exist, ultimately defining the clinical toxicology of the exposure. The fourth step is to

apply this general knowledge to the specific circumstances of the case at hand, incorporating the specifics of exposure, mitigating or exacerbating influences, individual susceptibilities, competing or synergistic causes, and any other relevant data.[112]

Many conditions resulting from toxic exposures are similar or identical in clinical manifestations to conditions arising from nontoxic causes.[113] Physicians rely on their training and expertise as clinicians and scientists when considering the medical and scientific literature as well as information about a patient's condition to best determine causality in a particular patient. Definitive tests for causality are actually rare,[114] and physicians must almost always use an element of judgment in determining the relationship between exposure and disease in a

112. Many cases involving issues of external causation have involved witnesses who testify to having arrived at an opinion on cause through a process of ruling out or eliminating other causes, a process frequently referred to by the courts and witnesses as "differential diagnosis" or "differential etiology" (for explanation of the differences between medical and legal uses of terminology, see section I.B., *supra*). Not infrequently, this form of testimony is implicitly or explicitly offered to satisfy the applicable burden of proof on causation. The relationship between the "more probable than not burden of proof" and "differential diagnosis" was discussed in *Cavallo v. Star Enterprise*, 892 F. Supp. 756 (E.D. Va. 1995), *aff'd in part, rev'd in part*, 100 F.3d 1150 (4th Cir. 1996), *cert. denied*, 522 U.S. 1044 (1998), a case in which the witness opined on whether a spill of aircraft fuel caused the plaintiff's rash. The court explained, "The process of differential diagnosis is undoubtedly important to the question of 'specific causation.' If other possible causes of an injury cannot be ruled out, or at least the probability of their contribution to causation minimized, then the 'more likely than not' threshold for proving causation may not be met." *Id.* at 771 (footnote omitted).

Courts differ on whether opinion based on such "differential diagnosis" or "differential etiology" of cause is admissible. *Compare* Westberry v. Gummi, 178 F.3d 257, 263 (4th Cir. 1999) (reliable "differential diagnosis" provides a valid basis for an expert opinion), Anderson v. Quality Stores, Inc., 181 F.3d 86 (4th Cir. 1999) (per curiam) (opinion on spray paint causing pulmonary problems should have been admitted based on "differential diagnosis" and temporal relationship), *In re* Paoli R.R. Yard PCB Litig., 35 F.3d 717 (3d Cir. 1994) (approving opinion based on "differential diagnosis"), *cert. denied*, 513 U.S. 1190 (1995), McCullock v. H.B. Fuller Co., 61 F.3d 1038, 1042–44 (2d Cir. 1995) (accepting opinion based on "differential etiology"), *and* Zuchowicz v. United States, 140 F.3d 381, 387–91 (2d Cir. 1998) (accepting witness's "differential etiology" opinion of causes of pulmonary hypertension), *with* Raynor v. Merrell Pharms., Inc., 104 F.3d 1371, 1375–76 (D.C. Cir. 1997) ("differential diagnosis" of cause of birth defect inadmissible where general causation proof absent), Cavallo v. Star Enter., 892 F. Supp. 756, 771–73 (E.D. Va. 1995) ("differential diagnosis" of cause inadmissible where general causation not established), *aff'd in part, rev'd in part*, 100 F.3d 1150 (4th Cir. 1996), *cert. denied*, 522 U.S. 1044 (1998), Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1412–14 (D. Or. 1996) ("differential diagnosis" and specific causation require proof of general causation; witness did not explain how he ruled out other causes), Haggerty v. Upjohn Co., 950 F. Supp. 1160, 1166–67 (S.D. Fla. 1996) ("differential diagnosis" testimony inadmissible where another cause could explain all of plaintiff's symptoms), *aff'd*, 158 F.3d 588 (11th Cir. 1998) (unpublished table decision), *and* Austin v. Children's Hosp. Med. Ctr., 92 F.3d 1185 (6th Cir. 1996) (unpublished table decision) (text at No. 95-3880, 1996 WL 422484, at *3 (6th Cir. July 26, 1996)) (expert unable to show that defendant, rather than other sources, "more likely than not" infected plaintiff's son with fatal virus).

113. *See, e.g.*, Herbert Y. Reynolds, *Interstitial Lung Disease*, *in* 2 Principles of Internal Medicine, *supra* note 42, at 1460, 1460–63 & tbl.259-1.

114. For a discussion of the difficulty of establishing causation, see Feinstein, *supra* note 40, at 266–74.

given patient. For instance, if a substance is suspected to cause an allergic or toxic condition, it may be necessary for diagnostic purposes to remove a patient from the workplace on a trial basis. On the other hand, determinations of external causation in patients with cancer may be irrelevant to treatment decisions as treatment is usually unaffected by assignment of cause.[115]

Physicians use both causal and probabilistic reasoning in determining both internal and external causation in regard to a particular illness. Methods for determination of some special external causes of disease may be found in occupational and environmental medical texts and journals[116] and generally are analogous to methods used for assessment of internal disease causation.[117] The difference is essentially in the body of medical, toxicological, epidemiological, and industrial hygiene knowledge that is relevant and needs to be incorporated.

For instance, in an elderly patient with chronic shortness of breath, the treating physician may use differential diagnosis to determine that chronic bronchitis is the best explanation as the underlying cause of symptoms, having excluded heart disease, anemia, lung fibrosis, and emphysema. The treating physician will rarely consider the external causes of the chronic bronchitis, beyond consideration of whether the patient smoked cigarettes.[118] The specific contribution of environmental or workplace exposures is rarely assessed as a part of clinical care in an elderly nonworking patient, since it does not affect diagnosis, treatment, and prognosis of this particular disease.[119] However, such determination of external causation may be essential to determination of a contested workers' compensation award.[120]

The key factor for the courts to recognize is that, while similar underlying reasoning is used in determination of both internal and external causation, and

115. However, exceptions may be cited, including the need to determine if there is a genetic (familial) risk of cancer that may require notification and screening of family members (e.g., certain forms of colon cancer and breast cancer), or if other family members or workers may be at remediable risk.

116. *See, e.g.*, Howard Hu & Frank E. Speizer, *Specific Environmental and Occupational Hazards, in* 2 Principles of Internal Medicine, *supra* note 42, at 2521, 2521–22; Linden & Lovejoy, *supra* note 76, at 2523–25; Hu, *supra* note 87, at 2565–67.

117. *See, e.g.*, peer review case studies published by the Agency for Toxic Substances and Disease Registry (ATSDR), a branch of the Centers for Disease Control and Prevention. For the most part, these case studies discuss the diagnosis and treatment of environmental illness, and in a number of instances discuss the reasoning involved in assessing the causal role of an environmental exposure. Selected ATSDR case studies are included in Environmental Medicine: Integrating a Missing Element into Medical Education, *supra* note 57, at app. C.

118. *See* Eric G. Honig & Ronald H. Ingram, Jr., *Chronic Bronchitis, Emphysema, and Airways Obstruction, in* 2 Principles of Internal Medicine, *supra* note 42, at 1451, 1452.

119. In a working patient, the contribution of workplace conditions may be taken into account in advising the patient on the advisability of returning to or remaining in the work environment if there are conditions present that may exacerbate the patient's respiratory condition. *Id.* at 1456.

120. *See, e.g.*, Fiore v. Consolidated Freightways, 659 A.2d 436 (N.J. 1995).

physicians routinely make limited determinations of external causation, many of the facts relevant to a determination of external causation rely on a body of scientific literature that is not routinely used by treating physicians. As a corollary, an expert's opinion on diagnosis and his or her opinion on external causation should generally be assessed separately, since the bases for such opinions are often quite different.

1. Exposure

Critical to a determination of causation is characterizing exposure. Exposure to a toxic substance can sometimes be established by a review of the patient's history and various available indicators of exposure, as discussed in section III. There are four "cardinal" pieces of exposure information:

1. The material or agent in the environmental exposure should be identified.
2. The magnitude or concentration of an exposure should be estimated, including use of clinical inference.
3. The temporal aspects of the exposure should be determined—whether the exposure was short-term and lasted a few minutes, days, weeks, or months, or was long-term and lasted for years. Similarly, the latency between exposure and disease onset is often critical.
4. If possible, the impact on disease or symptoms should be defined.[121]

In many instances, the desired information will be incomplete,[122] but it can often be inferred from the literature that a given amount of time in a particular industry is well associated with disease-producing potential. Progressive pulmonary fibrosis (accelerated silicosis) can develop in as little as ten months in workers involved in manufacturing abrasive soaps, tunneling in rock that has a high quartz content, or carrying out sandblasting in small, enclosed spaces, although

121. *See* Cullen et al., *supra* note 19, at 224.

122. The courts vary in the degree of certainty they require in exposure estimates. Many courts accept exposure evidence as sufficient without proof of specific levels. *See, e.g.*, Kannankeril v. Terminix Int'l, Inc., 128 F.3d 802, 808–09 (3d Cir. 1997). Other courts have required more particularized proof. *See, e.g.*, Curtis v. M&S Petroleum, Inc., 174 F.3d 661, 671–72 (5th Cir. 1999) (exposure evidence sufficient for opinion on causation where expert testified that refinery workers were exposed to at least 100 parts per million (ppm), and probably several hundred ppm, of benzene). Based on these measurements, *Curtis* distinguishes another Fifth Circuit case, *Moore v. Ashland Chemical, Inc.*, 151 F.3d 269 (5th Cir. 1998) (en banc), *cert. denied*, 119 S. Ct. 1454 (1999), in which exposure evidence was found insufficient to support an opinion on causation because the expert had a "'paucity of facts'" on which to base an opinion and did not testify to any specific levels of exposure. 174 F.3d at 670 (quoting *Moore*, 151 F.3d at 279 n.10). Exposure levels have been at issue in a number of other cases. *See, e.g.*, *In re* Paoli R.R. Yard PCB Litig., 916 F.2d 829 (3d Cir. 1990), *cert. denied*, 499 U.S. 961 (1991); *In re* "Agent Orange" Prod. Liab. Litig., 611 F. Supp. 1223 (E.D.N.Y. 1985), *aff'd*, 818 F.2d 187 (2d Cir. 1987), *cert. denied*, 487 U.S. 1234 (1988).

simple silicosis is much more commonly a chronic illness resulting from years of exposure.[123] In other situations, exposure estimates will be based on methods beyond the scope of medical expertise, such as physical or chemical analyses, or chemical fate-and-transport modeling (i.e., using mathematical models to project the movement of chemicals in air, water, and soil).

In determining causation, the physician may have particular insight into clinical clues related to exposure, such as clinical indicators of degree of exposure, temporal relationships, and the effect of removal from the toxic substance.[124] The physician also has particular insight into the role that preexisting illnesses may play in causing an exacerbation, recurrence, or complication of a clinical condition independent of any exposure to toxic products, or in concert with a toxic exposure.[125]

2. Reviewing the Medical and Scientific Literature

After characterizing exposure and the nature of the patient's disease, the physician expert witness must determine if the medical and research literature supports a determination of environmental causation.[126] The research literature in-

123. *See* Speizer, *supra* note 59, at 1431–32.

124. An appropriate temporal relationship—the time that elapsed between exposure and onset of disease or symptoms—is a necessary but often insufficient basis for an opinion on causation. Courts frequently warn against reasoning based on the premise "*post hoc, ergo propter hoc.*" *See, e.g.*, Whiting v. Boston Edison Co., 891 F. Supp. 12, 23 n.52 (D. Mass. 1995) (rejecting opinion on cause of acute lymphocytic leukemia following radiation exposure). In some cases, courts have permitted opinions on causation based primarily on temporal proximity between exposure and development of the disease, but many of these cases involved symptoms or diseases that closely followed the exposure asserted to be the cause. *See, e.g.*, Curtis v. M&S Petroleum, Inc., 174 F.3d 661, 670 (5th Cir. 1999); Anderson v. Quality Stores, Inc., 181 F.3d 86 (4th Cir. 1999) (unpublished table decision) (text at No. 98-2240, 1999 WL 387827, at *2 (4th Cir. June 14, 1999) (per curiam)). Other courts have excluded opinions on causation based primarily on temporal proximity. In *Moore v. Ashland Chemical, Inc.*, 151 F.3d 269, 278 (5th Cir. 1998) (en banc), *cert. denied*, 119 S. Ct. 1454 (1999), for example, the Fifth Circuit found that the expert's reliance on the temporal relationship between the exposure and the onset of symptoms was entitled to little weight in the absence of supporting medical literature. *See also* Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir.) (rejecting expert testimony on nicotine patch as cause of heart attack that occurred after three days of wearing patch), *cert. denied*, 519 U.S. 819 (1996); Porter v. Whitehall Labs., Inc., 9 F.3d 607, 614 (7th Cir. 1993) (rejecting clinical observations and temporal relationship between drug ingestion and renal failure as bases for opinion on causation where scientific studies unavailable). On occasion, a temporal relationship that does not fit the expected pattern may be a basis for ruling out the suspected cause. *See, e.g.*, Heller v. Shaw Indus., Inc., 167 F.3d 146, 157–58 (3d Cir. 1999) (temporal relationships may be important in supporting an opinion on causation, but expert's reliance on temporal relationship is flawed in this case). *See generally* Speizer, *supra* note 59, at 1429–36; Honig & Ingram, *supra* note 118, at 1452, 1456.

125. *See* Cullen et al., *supra* note 19, at 227.

126. The courts differ on the question whether the witness giving an opinion on causation must support his or her opinion with references to medical or scientific studies supporting a causal link between the toxic exposure and the plaintiff's disease. A number of courts have answered this question in the affirmative. *See, e.g.*, Moore v. Ashland Chem., Inc., 151 F.3d 269, 277–78 (5th Cir. 1998) (en banc), *cert. denied*, 119 S. Ct. 1454 (1999); Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir.)

cludes epidemiological studies and toxicology studies. The physician should be guided by the methods set forth in the Reference Guides on Epidemiology and Toxicology in evaluating this literature and its relevance to the patient's exposure and condition.[127]

Physicians also have access to case reports or case series in the medical literature. These are reports in medical journals describing clinical events involving one individual or a few individuals. They report unusual or new disease presentations, treatments, or manifestations, or suspected associations between two diseases, effects of medication, or external causes of diseases. For example, the association between asbestos and lung cancer was first reported in a 1933 case report, although the first controlled epidemiological study on the association was not published until the 1950s.[128] There are a number of other instances in which epidemiological studies have confirmed associations between a specific exposure and a disease first reported in case studies (e.g., benzene and leukemia; vinyl chloride and hepatic angiosarcoma),[129] but there are also instances in which controlled studies have failed to substantially confirm the initial case reports (e.g., the alleged connection between coffee and pancreatic and bladder cancer or the infectious etiology of Hodgkins disease).[130]

(witness cited no scientific or medical literature, or other explanation of asserted causal relationship between nicotine patch and heart attack), *cert. denied*, 519 U.S. 819 (1996); Porter v. Whitehall Labs., Inc., 9 F.3d 607, 615 (7th Cir. 1993) (medical literature did not establish link between ibuprofen and plaintiff's kidney ailment; medical theories had not been tested). Other courts have upheld the admission of medical opinion based solely on clinical observations and reasoning, sometimes with reference to the physician's experience with similar kinds of patients or cases. *See, e.g.*, Heller v. Shaw Indus., Inc., 167 F.3d 146, 153–57 (3d Cir. 1999); Westberry v. Gummi, 178 F.3d 257, 262–66 (4th Cir. 1999) (affirmed trial court's admission of expert testimony on talc as cause of plaintiff's sinus problems despite absence of supporting medical literature); Fadelalla v. Secretary of the Dep't of Health & Human Servs., No. 97-05730, 1999 WL 270423, at *6 (Fed. Cl. Apr. 15, 1999) (while clinical experience may be sufficient to establish causal relationship, in this case expert had insufficient clinical experience on which to base an opinion on causation); Becker v. National Health Prods., Inc., 896 F. Supp. 100, 103 (N.D.N.Y. 1995) (absence of published literature on relationship between diet supplement and diverticulosis not fatal to plaintiff's case where expert relied on "differential etiology").

127. *See* Michael D. Green et al., Reference Guide on Epidemiology, §§ V–VII, and Bernard D. Goldstein & Mary Sue Henifin, Reference Guide on Toxicology, §§ III–V, in this manual.

128. *See* Michael Gochfeld, *Asbestos Exposure in Buildings, in* Environmental Medicine, *supra* note 19, at 438, 440.

129. *See* Michael Gochfeld, *Chemical Agents, in* Environmental Medicine, *supra* note 19, at 592, 600 (vinyl chloride); Howard M. Kipen & Daniel Wartenberg, *Lymphohematopoietic Malignancies, in* Textbook of Clinical Occupational and Environmental Medicine 555, 560 (Linda Rosenstock & Mark R. Cullen eds., 1994) (benzene).

130. Kristin E. Anderson et al., *Pancreatic Cancer, in* Cancer Epidemiology and Prevention 725, 740–41 (David Schottenfeld & Joseph F. Fraumeni, Jr., eds., 2d ed. 1996); Debra T. Silverman et al., *Bladder Cancer, in* Cancer Epidemiology and Prevention, *supra*, at 1156, 1165–66.

Case reports lack controls and thus do not provide as much information as controlled epidemiological studies do.[131] However, case reports are often all that is available on a particular subject because they usually do not require substantial, if any, funding to accomplish, and human exposure may be rare and difficult to study. Causal attribution based on case studies must be regarded with caution. However, such studies may be carefully considered in light of other information available, including toxicological data.[132]

3. Clinical Evaluation of Information Affecting Dose–Response Relationships

Assessing the role of external causes in the patient's condition requires the integration of the information described in the preceding sections, with particular attention to dose–response relationships. The toxicological law of dose–response, that is, that "the dose makes the poison," refers to the general tendency for greater doses of a toxin to cause greater severity of responses in individuals, as well as greater frequency of response in populations.[133] Clinically, there are some instances in which the general rule does not hold. For agents that cause an allergic response through an immunologic mechanism, the dose–response relationship is often less straightforward. Many people who are not prone or able to develop an allergic reaction, for genetic or other reasons, will not respond adversely to the substance at any dose. However, those who are susceptible are more likely to become specifically reactive (sensitized) to the specific agent as the dose increases. After sensitization has occurred, severe reactions may occur with exposures that are much lower than the previous level required for sensitization.[134]

Although some diseases (e.g., pneumonia that is due to influenza) are frequently considered to be unifactorial, the possibility of multiple causes of a clini-

131. *See generally* Michael D. Green et al., Reference Guide on Epidemiology § II.A, in this manual.

132. *See* Cullen et al., *supra* note 19, at 226. Courts have given varying treatment to case reports. *Compare* Haggerty v. Upjohn Co., 950 F. Supp. 1160, 1165 (S.D. Fla. 1996) (case reports are "no substitute for a scientifically designed and conducted inquiry" (citing Casey v. Ohio Med. Prods., 877 F. Supp. 1380, 1385 (N.D. Cal. 1995))), *aff'd*, 158 F.3d 588 (11th Cir. 1998) (unpublished table decision), *and* Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1411 (D. Or. 1996) (case reports "cannot be the basis of an opinion based on scientific knowledge"), *with* Pick v. American Med. Sys., Inc., 958 F. Supp. 1151, 1160–62, 1178 (E.D. La. 1997) (case studies on gel implants admissible in case on penile implant; theory developed by single physician not admissible), Glaser v. Thompson Med. Co., 32 F.3d 969, 975 (6th Cir. 1994) (ordering trial based on witness who relied on case reports and his own research in rendering opinion on diet pills as cause of intracranial bleeding and fall), *and* Cella v. United States, 998 F.2d 418, 426 (7th Cir. 1993) (in claim under Jones Act, medical opinion on cause of polymyositis based in part on case reports).

133. *See* Michael Gochfeld, *Principles of Toxicology, in* Environmental Medicine, *supra* note 19, at 65, 71–72.

134. *See* Cullen et al., *supra* note 19, at 228–29.

cal condition is a critical concern. At some level most diseases have multiple host and environmental factors that contribute to their presence. A commonly held misconception is that the presence of a nontoxic or other toxic cause for a condition automatically excludes a role for the toxin being considered as an external cause.[135] While this is sometimes true, in reality the converse can also be true. For example, epidemiology studies dealing with occupational asbestos exposure and cigarette smoking indicate that together they result in much higher rates of lung cancer than either one causes on its own.[136] Thus, two toxic agents have been found to interact in a synergistic manner so that their combined effects are much greater than even the sum of their individual effects.[137]

Even if causal factors do not interact synergistically, several may contribute in an incremental fashion to a disease and should not be assumed to be mutually exclusive.[138] Accordingly, the common statement that "alternative causes of disease must be ruled out" before causation is attributed can be more accurately refined to say that "the role of other causes must be adequately considered." If there is a significant rate of disease of unknown etiology (i.e., other causes or risk factors have not been identified), the determination of external causation

135. Some courts have stated that the plaintiff must offer a "differential diagnosis" to rule out other causes, whereas other courts have rejected such a requirement. *Compare* Wheat v. Pfizer, Inc., 31 F.3d 340, 342 (5th Cir. 1994) (witness failed to rule out hepatitis C and another drug as causes of plaintiff's liver disease), Mancuso v. Consolidated Edison Co., 967 F. Supp. 1437, 1446 (S.D.N.Y. 1997) ("differential diagnosis" required to rule out other possible causes; plaintiff's complaints were commonplace ailments), *and* National Bank of Commerce v. Dow Chem. Co., 965 F. Supp. 1490 (E.D. Ark. 1996) (case dismissed because, inter alia, plaintiffs failed to exclude other causes), *aff'd*, 133 F.3d 1132 (8th Cir. 1998), *with* Curtis v. M&S Petroleum, Inc., 174 F.3d 661, 670–72 (5th Cir. 1999) (rejecting requirement of "differential diagnosis" to rule out other causes), *and* Heller v. Shaw Indus., Inc., 167 F.3d 146, 153–57 (3d Cir. 1999) (existence of possible alternative causes goes to weight, not admissibility).

136. Occupational asbestos exposure in nonsmokers increases the risk of lung cancer by a factor of about five, from about 11 per 100,000, for nonsmoking industrial workers not exposed to asbestos to about 58 per 100,000 for nonsmoking asbestos workers; a significant smoking history increases the rate of lung cancer by a factor of at least ten. *See* U.S. Surgeon Gen., U.S. Dep't of Health & Human Servs., The Health Consequences of Smoking: Cancer and Chronic Lung Disease in the Workplace 216 (1985); *see also* Rodolfo Saracci, *The Interactions of Tobacco Smoking and Other Agents in Cancer Etiology*, 9 Epidemiologic Revs. 175, 176–80 (1987). Because the effects of smoking and asbestos are multiplicative for lung cancer, the population of smoking asbestos workers has a lung cancer incidence of 5 times 10, or 50 times the background rates, rather than the 15-fold increase predicted by adding the separate risks. *See* U.S. Surgeon Gen., U.S. Dep't of Health & Human Servs., *supra*, at 216–17.

137. *See* Gochfeld, *supra* note 133, at 73.

138. For example, both occupational asthma and smoking can lead to impairment of pulmonary function, and the presence of one does not rule out a causal role for the other. *See* John H. Holbrook, *Nicotine Addiction*, *in* 2 Principles of Internal Medicine, *supra* note 42, at 2516, 2518; E.R. McFadden, Jr., *Asthma*, *in* 2 Principles of Internal Medicine, *supra* note 42, at 1419, 1419–21. *Cf.* Wheat v. Pfizer, Inc., 31 F.3d 340 (5th Cir. 1994), which involved a victim who died of hepatitis after taking two drugs known to cause liver damage. As to her claim against Pfizer, the manufacturer of one of the drugs, the court found the evidence inadequate, in part, for failing to exclude the possibility that her disease was caused by the other drug. *Id.* at 343. The plaintiff's witness offered the possibility that the hepatitis

may be complicated.[139] In general, if a patient is not subject to other known risk factors for a disease, it is more likely that the external cause is a factor in causing the patient's illness.[140]

Differences in individual susceptibility are commonly cited as the reason why one person gets sick from an environmental exposure while other persons are not affected. True individual susceptibility is based on genetic differences, such as immunologic reactivity, enzyme metabolism, and gender.[141] A number of other acquired factors, such as age, body mass, interacting simultaneous exposures, and preexisting disease, may also contribute to susceptibility.[142] Reliable and accurate information is available about the effects on some diseases of age, body mass, gender, and other factors; however, information on genetic susceptibility is available for only a few diseases, and information on the relation between genetic susceptibility and particular toxic exposures, for even fewer.[143]

resulted from the combined action of the two drugs, which the court rejected because the witness cited no study of the combined effects of the drugs. *Id.* The court also faulted the plaintiff for failing to rule out hepatitis C as a cause of the liver damage, though there was no test for the condition at that time. *Id.* at 342. *But see* Benedi v. McNeil-PPC, Inc., 66 F.3d 1378, 1384 (4th Cir. 1995) (upholding plaintiff's recovery for liver damage caused by Tylenol and alcohol consumption).

139. The problem of unidentified risks (often termed "background cases of unknown etiology") has been recognized in a number of decisions. For example, in *In re Breast Implant Litigation*, 11 F. Supp. 2d 1217 (D. Colo. 1998), the court disapproved of a physician's identification of silicone as the cause of the plaintiff's disease through "differential diagnosis," stating: "As a practical matter, the cause of many diseases remains unknown; therefore, a clinician who suspects that a substance causes a disease in some patients very well might conclude that the substance caused the disease in the plaintiff simply because the clinician has no other explanation." *Id.* at 1230. *See also* National Bank of Commerce v. Dow Chem. Co., 965 F. Supp. 1490 (E.D. Ark. 1996) (rejecting testimony that pesticide caused birth defect where witness acknowledged that causes are unknown for 70% to 80% of birth defects), *aff'd*, 133 F.3d 1132 (8th Cir. 1998); Whiting v. Boston Edison Co., 891 F. Supp. 12 (D. Mass. 1995) (in case alleging radiation caused power plant worker's acute lymphocytic leukemia, witness's acknowledgement that 90% of cases are of unknown cause cast doubt on "differential diagnosis" of cause); *In re* "Agent Orange" Prod. Liab. Litig., 611 F. Supp. 1223, 1250 (E.D.N.Y. 1985) ("Central to the inadequacy of plaintiffs' case is their inability to exclude other possible causes of plaintiffs' illnesses—those arising out of their service in Vietnam as well as those that all of us face in military and civilian life."), *aff'd*, 818 F.2d. 187 (2d Cir. 1987), *cert. denied*, 487 U.S. 1234 (1988). The plaintiff may be able to rely on inferences from epidemiological, toxicological, or other evidence, however. *See* Michael D. Green et al., Reference Guide on Epidemiology, and Bernard D. Goldstein & Mary Sue Henifin, Reference Guide on Toxicology, in this manual; *In re* Hanford Nuclear Reservation Litig., No. CV-91-3015-AAM, 1998 WL 775340 (E.D. Wash. Aug. 21, 1998).

140. This kind of reasoning is discussed in *In re Paoli Railroad Yard PCB Litigation*, 35 F.3d 717, 760 n.30 (3d Cir. 1994), *cert. denied*, 513 U.S. 1190 (1995).

141. *See* Stuart M. Brooks et al., *Types and Sources of Environmental Hazards*, *in* Environmental Medicine, *supra* note 19, at 9, 15–17; Daniel W. Nebert et al., *Genetic Epidemiology of Environmental Toxicity and Cancer Susceptibility: Human Allelic Polymorphisms in Drug-Metabolizing Enzyme Genes, Their Functional Importance, and Nomenclature Issues*, 31 Drug Metabolism Revs. 467 (1999); Maurizio Taningher et al., *Drug Metabolism Polymorphisms as Modulators of Cancer Susceptibility*, 436 Mutation Res. 227 (1999).

142. *See* Karen Reiser, *General Principles of Susceptibility*, *in* Environmental Medicine, *supra* note 19, at 351, 351–52, 358.

143. *See id.* at 357.

In almost all instances, integration of all the above factors into an opinion on causality cannot be reduced to mathematical formulas. There are inevitable gaps in information, as well as lack of knowledge regarding individual characteristics, such as susceptibility and resistance. Thus, clinical judgment is critical to opinions on diagnosis and causation for the individual patient even when the scientific population basis for general causation may be quite strong.

V. Treatment Decisions

Following diagnosis, most physicians are concerned with applying appropriate treatment to either cure or ameliorate a patient's condition. Such treatment may be surgical (e.g., removal of a diseased organ), ablative (e.g., radiotherapy aimed at a tumor), chemotherapeutic (e.g., use of pharmacological agents with a host of different actions), rehabilitative (e.g., physical therapy), interdictive (e.g., removal of the patient from a toxic or allergenic exposure), behavioral (e.g., counseling), or something else.[144] Some of the recommended therapies for different conditions found in the textbooks and professional literature are reified as practice guidelines by various organizations and the government. Some recommended therapies have demonstrated their effectiveness in randomized controlled trials, whereas others, both old and new, have much less scientific support.

Treatment options for an individual patient must be assessed in light of the nature and severity of the particular disease (e.g., people whose lung cancer is metastatic are not often candidates for removal of the primary tumor), and the likelihood of unacceptable complications from the treatment (e.g., removal of a lung to cure cancer in someone with severe emphysema may not leave enough remaining lung tissue to allow the patient to walk, even if his or her cancer is cured).[145] Prediction of the effects, both positive and negative, of a course of therapy is based on the professional literature and consideration of a patient's specific situation. For example, a patient with underlying kidney disease may not be an appropriate candidate for some radiographic tests and therapies that use dye that runs a high risk of causing further damage to the kidneys. Use of an effective antibiotic to which a patient "may possibly" have had a previous aller-

144. *See* Kassirer & Kopelman, *supra* note 48, at 11, 32–33.

145. A physician's selection of appropriate treatment is often at issue in medical malpractice cases (*see supra* notes 31–32 and accompanying text), but it also is at issue in other kinds of cases, including claims that medical treatment was "necessary" and therefore covered in insurance litigation under ERISA (*see, e.g.*, McGraw v. Prudential Ins. Co., 137 F.3d 1253, 1258–1263 (10th Cir. 1998)), claims that treatment was improperly withheld from prisoners under the Eighth Amendment (*see, e.g.*, Kulas v. Roberson, 202 F.3d 278 (9th Cir. 1999) (unpublished table decision) (text at No. 98-16954, 1999 WL 1054663 (9th Cir. Nov. 19, 1999) (mem.)), and medical monitoring claims (*see, e.g.*, *In re* Paoli R.R. Yard PCB Litig., 916 F.2d 829, 852 (3d Cir. 1990), *cert. denied*, 499 U.S. 961 (1991)).

EXHIBIT E

ASSESSMENT OF THE POTENTIAL RISKS TO HOMEOWNERS AND RESIDENTIAL CONTRACTORS FROM ASBESTOS EXPOSURE ASSOCIATED WITH VERMICULITE ATTIC INSULATION

REPORT BY:
ELIZABETH L. ANDERSON, Ph.D., A.T.S Fellow

DATE:
April 14, 2003

QUALIFICATIONS

1. I am the President and Chief Executive Officer of Sciences International, Inc., a company of scientists dedicated to health and environmental assessment.

2. I have a Ph.D. in organic chemistry and am a Fellow of the Academy of Toxicological Sciences. Formerly, I spent 14 years at the U.S. Environmental Protection Agency (EPA), from October 1971 to December 1985, where I directed EPA's central risk assessment programs for the last 10 years of my tenure. Specifically, in 1975, I became the Executive Director of an intra-Agency committee that was commissioned to write an Agency cancer policy. This committee developed the Agency's first risk assessment guidelines for assessing risk associated with exposure to suspected carcinogens in the environment. Subsequently, in 1976, I established EPA's first Carcinogen Assessment Group (CAG) which formed the core for the enlarged office, the Office of Health and Environmental Assessment (OHEA), now called the National Center for Environmental Assessment, which was established in 1978. As the director of the first CAG and then OHEA, I had responsibility for the central risk assessment activities of EPA for 10 years before I left the Agency. The primary functions of this office were to conduct assessments and establish the toxicity of a wide variety of toxic agents, provide leadership to establish EPA-wide guidelines for toxicity and risk assessments, and oversee EPA's health assessment programs. Of particular relevance to the issues herein addressed, my office was responsible for the risk assessment of toxic air pollutants and for writing the National Ambient Air Quality Criteria Documents. During my tenure as the director of OHEA, I was

responsible for the draft document, Airborne Asbestos Health Assessment Update (EPA, 1986), which was published in June 1986, shortly after my departure.

3. Since leaving EPA, I have continued active participation in the sciences of health and environmental risk assessment. For example, I am past-President of the Society for Risk Analysis; and am currently Editor-in-Chief of the journal, *Risk Analysis: An International Journal*, which is the leading peer-reviewed international journal on topics of risk assessment. I regularly serve on expert peer review and advisory committees on risk assessment topics for the EPA and other organizations including current appointments to the Department of Energy's Los Alamos National Laboratory Expert Advisory Committee, a recent expert committee for the National Academy of Sciences, and an EPA expert committee that is exploring ways to improve EPA's repository of toxicological and risk information called the Integrated Risk Information System (IRIS). My curricula vita, including a list of my publications for the last ten years, is provided in Appendix A. A list of recent depositions and trial testimony is provided in Appendix B. My compensation is provided in Appendix C.

4. I am submitting this report at the request of WR Grace to address issues associated with vermiculite attic insulation. If new information becomes available that is relevant to the issues discussed in this report, I reserve the right to supplement the report.

EXECUTIVE SUMMARY

I have reviewed the available scientific data and studies related to asbestos exposures and risks associated with vermiculite attic insulation (VAI), and I have reviewed the relevant documentation and data provided by the claimants. I have also conducted a risk assessment to estimate the potential risks associated with VAI for residents and contractors. From this review and analysis, I have reached the following conclusions.

Conclusion 1: Health risk assessment is the scientifically appropriate and accepted methodology for assessing the potential cancer risk associated with VAI.

Risk assessment is the scientifically accepted process for assessing whether exposure to an environmental substance has a significant potential to cause adverse health effects. Risk assessment is routinely applied by Federal, state and local U.S. governmental organizations and international organizations, and is well accepted in the scientific community. In the risk assessment process, the estimated exposure of an individual takes into account the concentration, frequency and duration of exposures to a particular substance. The resulting exposure assessment for carcinogens includes a time-weighted average for a lifetime exposure and is compared with health effects data relating to the potential effects associated with a given exposure. From this comparison, the risk of individuals for adverse health effects is estimated.

Conclusion 2: I have evaluated the available exposure data from VAI disturbance activities and conducted a risk assessment according to accepted methodology with the useful data. The risks for residents are very low, and not of significant concern. The risks for contractors are higher than for residents, but are still below risk levels routinely accepted in the regulatory community or experienced in daily activities, and not of significant concern.

Seven modern studies were identified that provide personal exposure measurements for individuals engaging in activities that could lead to potential VAI exposure. Of these studies, three were found to be useful for risk assessment, and one other was found to be useful, but with caution. There are not specific studies available to estimate the amount of time residents and contractors may come into contact with VAI. Therefore, conservative assumptions were made about typical and high-end exposure durations for a variety of activities that may involve disturbance of VAI. These exposure frequency and duration estimates were combined with the personal exposure data to estimate typical and high-end lifetime average exposures to asbestos. The exposure estimates were compared

with a cancer potency value developed by the U.S. Environmental Protection Agency (EPA) to estimate the lifetime risk of cancer associated with VAI exposures. In general, the risk assessment employed conservative assumptions (i.e., assumptions that would tend towards overestimating risk), which must be accounted for in interpreting the results.

The estimated risks for residents were very low, and not a significant concern compared to the range of risks considered acceptable by the EPA and were lower than many other environmental risks and other common risks routinely accepted by people in their everyday lives. For contractors, the risks were higher than residents because the assumed exposure frequency and durations were higher. However, when making reasonable assumptions, the estimated risks were within ranges considered acceptable by EPA and below risk levels that are routinely accepted by the Occupational Safety and Health Administration (OSHA) for worker protection, and lower than many other occupational risks.

Conclusion 3: The EPA, with its contractor Versar, has also conducted a risk assessment for residents that engage in activities that disturb VAI, and found that the risks were within ranges considered acceptable.

In addition to the risk assessment presented in this report, the EPA recently conducted its own assessment for residents exposed to VAI. The study was conducted by Versar, an EPA contractor, and I have reviewed a draft of the study. This assessment showed that the risks to residences are low. There were some flaws with the risk estimates in that study that are discussed in this report, and the fiber counts were likely overestimated because cleavage fragments may have been counted and indirect preparation techniques may been used, both factors that artificially increase the risk estimates. These factors suggest that, despite the low risk estimates, the risks found in the EPA study are overestimates. This study may be regarded as a useful screening study (i.e., with a conservative, health protective approach, low risks were found). These findings are consistent with the results of my assessment.

Conclusion 4: The Agency for Toxic Substances and Disease Registry (ATSDR) recently conducted a medical monitoring study of residents of Libby, Montana. This epidemiologic investigation found that there was not an association between potential health impacts with residents having VAI in their homes or engaging in activities that disturbed the VAI.

In this medical monitoring study, ATSDR conducted chest radiographs and spirometry testing on a subpopulation of Libby residents that included 6,149 current or former

residents of Libby and the surrounding area. The study also included a questionnaire about potential exposure pathways for each resident. ATSDR conducted a correlation analysis of the medical and questionnaire to determine which exposure pathways were associated with evidence of asbestos exposure in the lung or decrements in lung function. Neither having VAI in a home nor handling VAI was associated with any effects. This provides more evidence that the risks to residents associated with VAI are not significant.

Conclusion 5: The findings from my risk assessment, the EPA/Versar risk assessment, and the ATSDR medical monitoring study are all consistent. The risks associated with VAI exposures are low, and are of a magnitude that is lower or similar to risks that are routinely experienced by individuals for environmental causes and other common activities, and accepted by regulatory agencies in setting standards.

The findings of my risk assessment, the EPA/Versar risk assessment, and the ATSDR medical monitoring study all show that the risks to residents associated with VAI are not significant. The consistency between these three studies provides a strong weight-of-the-evidence in support of this conclusion.

Additionally, the low risks that were estimated for residents and contractors are similar to or less than risks that are commonly experienced and accepted by individuals and regulatory agencies, both as the results of environmental causes or other common activities. In addition, the resulting risks are within the acceptable target range of risk, 10^{-4} to 10^{-6}, commonly accepted by EPA and far below risk levels associated with OSHA standards for worker protection.

Conclusion 6: The claimants have not conducted a risk assessment. Therefore, the claimants have not provided a scientific basis for showing that there are risks associated with VAI.

The claimants have not assessed the risk associated with VAI. For the most part, the claimants have presented some personal exposure data, without providing any context for how the data should be interpreted. There is a common saying in the medical literature: "the dose makes the poison," which dates back to the Enlightenment. This reference essentially means that the potential for disease from any type of exposure is a function of the frequency, duration, and magnitude of the exposure. In one case, the claimants compared some old measurement data to an OSHA standard that applies to workers. However, this OSHA standard is intended to protect workers routinely exposed to asbestos, as opposed to the infrequent exposures associated with VAI, and it is inappropriate to imply anything about risk from this comparison as time-weighted

averages for lifetime exposure (total dose averaged over a lifetime) have not been considered. Otherwise, the claimants have not attempted to show that the exposures that they measured may result in any adverse effects. Therefore, the claimants have not provided any scientific evaluation to show that exposures to VAI are harmful.

I. Vermiculite was commonly used as attic insulation. Some vermiculite attic insulation (VAI) that was sold by Grace contained small amounts of asbestos, and there is a potential for exposure to this asbestos. This report presents an assessment of the potential human health risks associated with VAI.

Vermiculite is a naturally occurring mineral that has been used in construction, insulation, and gardening products. When expanded, it has a shiny appearance and looks like small pieces of popcorn. Its light weight and structure make it a good insulation product, but also make it possible for some vermiculite to become airborne during a disturbance. Until 1984, Grace sold expanded vermiculite as attic insulation under the product name Zonolite.

The vermiculite used in Zonolite came from a mine in Libby, Montana. The ore from this mine contained a natural deposit of amphibole[1] minerals. Prior to being included in VAI, vermiculite was subjected to various production processes designed to remove naturally occurring impurities, including tremolite (2/5/03 Wood Dep. at 14-15). These processes involved, among other things, extensive use of screening and floatation devices at the Libby mine and mill as well as further screening at expansion plants and removal of fibers, including tremolite, during the expansion process itself. (2/26/03 Wolter Dep. at 28-30; 2/03 Yang Dep. at 26-28). Small amounts of asbestos may still be present in VAI that originated from the Libby mine. When left undisturbed, there is little, if any, chance for asbestos exposure. However, when disturbed through various activities in the attic, there is a potential for exposure to airborne asbestos fibers, but the levels of exposure are likely to be very low.

Asbestos is found in a variety of other materials that have been used in buildings, such as fireproofing materials, pipe insulation, air supply duct wrap, boiler insulation, and others (CPSC, 1979). Some of these materials contain up to 90% asbestos, and have been the historical motivation for the concern about asbestos exposures in buildings. Nonetheless, EPA generally recommends that these products not be removed from buildings, as long as the products are stable, because removal could ultimately lead to higher exposures (EPA, 1990). On the other hand, VAI generally contains less than 1% asbestos. By EPA regulations, products with less than 1% asbestos are not considered asbestos products for regulatory purposes (EPA, 1984; EPA, 1990a).

[1] Amphibole refers to a particular type of mineral that contains asbestos.

This report addresses the risks associated with the VAI exposure pathway by applying commonly accepted methods for estimating and characterizing health risks. Risks to homeowners with VAI in their residences and risks to contractors that perform tasks in homes with VAI are considered.

II. Risk assessment is the accepted scientific method for evaluating the plausibility of an environmental exposure causing a disease, and can be specifically applied to estimate the potential for health impacts during disturbances of VAI. Risk assessment is a scientific, rigorous methodology that is widely accepted in the scientific community and by state, Federal, and international organizations. However, the claimants' experts have not conducted risk assessment. Therefore, the claimants have not provided an analysis that meets minimum scientific standards for demonstrating that exposures associated with VAI are harmful.

A. Risk assessment is the scientifically appropriate method for assessing the likelihood that environmental exposures are associated with disease, and can be applied to investigate the plausibility that disturbance of VAI will lead to adverse health effects.

A health risk assessment can establish if an exposure is at least plausibly linked to adverse health effects. In a risk assessment, the estimated exposures are compared to health benchmarks to determine the likelihood that the exposure could result in an adverse health effect. Risk assessment is a scientifically accepted methodology that is widely used by U.S. Federal, state, and local agencies, and international organizations to address issues of potential health effects.

The claimants' experts in this case have not conducted a health risk assessment to determine the plausibility of health effects associated with VAI exposure. Therefore, they have failed to provide any scientific basis for showing the plausibility of adverse health effects associated with VAI exposure.

B. The National Research Council of the National Academy of Sciences established a paradigm for conducting risk assessments, which is widely accepted by the scientific community and applied by governmental organizations in the U.S. and internationally.

In 1983, the National Research Council (NRC) published a document entitled *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983).

At the time, I was the Director of the Office of Health and Environment Assessment at the EPA, and I served as an advisor to the committee and a reviewer for this document. The document established health risk assessment as the acceptable approach for assessing risk associated with exposure to environmental substances. It is now considered an essential text for health risk assessment. The document outlined a four-step process for risk assessment:

1) *Hazard identification*: the identification of a compound as a potential hazard based on animal toxicity studies or human epidemiologic studies.
2) *Dose-response assessment*: the assessment of the dose required to cause particular health effects.
3) *Exposure assessment*: an estimation of the exposure of the compound from the particular activity in question.
4) *Risk characterization*: characterization of the evidence that an agent might be a human carcinogen (or cause other noncancer effects) together with a comparison of the exposure and dose-response to estimate the potential risk, accounting for uncertainties.

This four-step process is now often referred to as the "risk paradigm," and is widely accepted and applied by governmental authorities throughout the world and by the scientific community.

C. *The claimants in this case did not conduct a risk assessment, and have not provided any rigorous analysis that demonstrates the plausibility that exposures from VAI disturbances will lead to adverse health impacts. The only attempt by the claimants to associate VAI exposure with such adverse health effects was to compare airborne measurement data with the Permissible Exposure Limit (PEL) from the Occupational Health and Safety Administration (OSHA) and make inappropriate implications from this comparison.*

Claimants' expert Mr. Ewing compared exposure measurements during VAI installation simulations conducted by WR Grace in the 1970s to the OSHA PEL at the time (see Ewing expert report, pages 15-17) and drew inappropriate conclusions from this comparison. Further, Mr. Ewing notes that the current OSHA PEL is lower (i.e., more restrictive).

However, as Mr. Ewing states, the OSHA standards do not apply to homeowners. The PEL is set to protect workers, and is currently set at 0.1 fiber/cc over an 8-hour average period (i.e., a workday). As a regulatory standard, the PEL is based

on a concentration averaged over a workday. However, the cancer risk associated with asbestos exposure is not determined by looking at the exposure in a single day. Instead, the risk is determined as a function of the frequency, magnitude, and duration of exposure over a lifetime. OSHA recognized this in setting the current PEL. In developing the PEL, OSHA developed a dose-response model to assess the risk (or the individual probability of mortality from cancer) as a function of asbestos exposure. In its 1984 rulemaking, OSHA presented risks for workers exposed for 1, 20, and 45 years of full-time employment in a workplace with potential asbestos exposure (U.S. Department of Labor, 1994). Thus, the PEL is designed to reduce the risks of workers that are continuously exposed to asbestos over a long period of time. For infrequent exposures, it is inappropriate to imply that exceeding the PEL will result in any adverse health effects. The use of a dose-response model that is based on lifetime exposure is the most scientifically accurate way to assess the risks associated with infrequent exposures.

The exposure durations considered by OSHA for workers in a job that will result in routine exposure to asbestos are appropriate. However, it is unlikely for residents with VAI in their homes to be routinely exposed to asbestos at a frequency and duration of a person in a workplace with asbestos. Instead, most homeowners are likely to be exposed just a few times a year when they go into their attic and perform tasks, such as moving boxes that may result in a disturbance of the VAI. For homeowners involved in renovation activities, these tasks may be performed more frequently than for the typical homeowner, but the frequency and duration of exposure would still not present a significant risk. Additionally, for some of the tasks that may result in the highest exposures such as clearing or removing the VAI, the homeowner exposure frequencies are even lower. With respect to the removal of VAI, it is likely that a resident would only remove VAI, if at all, once or twice in their lifetime.

For a contractor that performs work in homes that have VAI, the exposure frequencies will likely be higher than most residents. However, most homes do not have VAI. The EPA estimates that about 1 million homes in the United States contain VAI (Versar, 1982). As Zonolite was not sold after 1984, this EPA estimate is likely a reasonable value for homes with VAI that contain any Libby amphiboles. Furthermore, most contracting activities do not take the contractor into the attic to perform a task that may result in disturbances of VAI. There are a series of events that must happen for a contractor to be exposed to VAI:

1) The contractor must go to a job at an older home, as homes built after 1984 would not have VAI.
2) The older home must have VAI. There are several other types of insulation that have been or currently are used. Only about 1% of homes in the U.S. have VAI.
3) The contractor must engage in an activity that disturbs the VAI. Many contracting activities do not take place anywhere near the attic, such as renovations in the living area or work on the exterior of the home. To disturb the VAI, the contractor must either engage in an activity in the attic (and spend a significant amount of time there for any significant exposure) or engage in some other activity that disturbs the insulation, such as drilling a hole in the ceiling below the attic.

All of these events must occur together for there to be an exposure to VAI.

III. The risk assessment paradigm is the only accepted methodology that can be used to address risk associated with exposure to VAI.

A. <u>Hazard Identification</u>: *The weight-of-evidence that asbestos causes cancer in humans is based on a series of epidemiologic studies in which workers have been exposed to asbestos at high concentrations, with frequent exposures over a considerable period of time or for individuals that were similarly exposed. The observed health effects associated with asbestos exposure include lung cancer and mesothelioma, and noncancer effects such as asbestosis.*

It is widely known and accepted that repeated exposures to high levels of asbestos over a long period of time may result in lung cancer and mesothelioma, which is a cancer of the pleural lining of the lung. The EPA classifies asbestos as a Class A carcinogen, or a known human carcinogen based on epidemiologic data gathered from exposures in the workplace[2]. Additionally, repeated exposure to high levels of asbestos is associated with asbestosis, a chronic inflammation of the lung.

The health effects associated with asbestos exposure are known as the result of numerous epidemiologic studies on workers in the asbestos industry, who were exposed to very high levels of asbestos over long periods of time. Additionally, some of these epidemiologic studies were done on miners or other workers exposed specifically to Libby amphiboles (McDonald et al., 1986; Amandus et

[2] http://www.epa.gov/iris/subst/0371.htm

al., 1987), providing evidence that Libby amphiboles are a health risk at high exposures that are sustained over a long period of time.

B. *Dose-response assessment: The EPA has published a review of asbestos health effect studies and has developed a recommended potency value for estimating the theoretical risk associated with a given asbestos exposure. Use of the EPA cancer potency value provides a conservative, upper-bound estimate of the risk.*

Simply stating that asbestos is associated with adverse health impacts is not sufficient to conclude that there will be adverse health effects associated with exposure from disturbing VAI. The manifestation of adverse health impacts depends upon the frequency, duration, and magnitude of exposure, or sometimes commonly said as "the dose makes the poison." The asbestos exposure associated with VAI is substantially lower than the exposures of the asbestos workers that were found to have elevated levels of disease. Therefore, it is necessary to estimate the likelihood of adverse health effects as a function of the actual exposure to asbestos from VAI.

EPA evaluates the available health effects data for environmental contaminants, and develops potency values that can be used for risk assessment. These reviews are cataloged into EPA's Integrated Risk Information System (IRIS). IRIS is widely used by EPA for internal risk assessments used in the regulatory decision-making process. IRIS is also frequently used by other governmental agencies and by members of the scientific community.

EPA has an IRIS file for asbestos which reviews the available human epidemiologic and animal toxicology data and recommends a cancer risk value of 0.23 per fiber/ml, based on the human epidemiologic data and using an exposure metric called PCM-equivalent (discussed in the exposure assessment section that follows). The value represents a probability of developing cancer for a lifetime average exposure of 1 fiber/ml. It is important to note that the risk factor is conservative and only to be compared with the average exposure over a lifetime. Therefore, periods where there is no exposure to asbestos must be accounted for when developing this average value. The occurrence of cancer from environmental exposures is generally the result of prolonged, elevated exposures. Thus, the total exposure over a lifetime must be taken into account.

The EPA cancer risk potency represents a theoretical risk that is likely higher than the actual risk, particularly for the low exposures associated with VAI. For

example, in the EPA model, the cancer risk is assumed to be linear with exposure; thus, for example, if the exposure is decreased by 6-fold, the risk is also assumed to decrease 6-fold. This approach was adopted by the EPA in 1976 to place a plausible upper-bound on the risk, meaning that the real risk could be considerably lower, even approaching zero. In fact, at doses lower than those in the epidemiologic studies used to estimate the IRIS potency factor, the risk is unknown and could be considerably lower even approaching zero. The linear assumption is conservative, and is made to be precautionary and public health protective as prescribed by environmental statutes. As an example, for a person with a lifetime average exposure to asbestos of $4.3x10^{-6}$ fibers/ml, the theoretical cancer risk would be 1 in a million as follows:

$$4.3x10^{-6}\ \frac{fibers}{ml}[exposure] * 0.23\frac{ml}{fiber}[risk\ factor] = 10^{-6}[risk\ estimate]$$

However, it is possible that the risk is lower or approaching zero at this low level of exposure. Currently, there is no other available methodology for assessing the risks of low-level asbestos exposures. However, if a method is developed, I may reserve the right to update this analysis.

The level of exposure that causes asbestosis is generally considered higher than the level that causes cancer. Therefore, a risk assessment based on cancer potency should also be protective for asbestosis (Berman and Crump, 2001).

The same methods that were used to develop the EPA cancer potency value in IRIS were applied to the epidemiologic studies specific to the Libby amphiboles in VAI (Moolgavkar, 2002). The estimated potency values were similar or lower than the IRIS value, which suggests that Libby amphiboles are of similar or lower potency than the types of asbestos used to develop the EPA potency factor.

C. *Exposure assessment: There are several studies that have been conducted that have measured exposures during disturbance of VAI. However, the nature of the sample collection and asbestos measurement methodology is important for assessing the appropriateness of any measurement data for use in a scientifically reliable risk assessment.*

The available measurement studies of exposure during VAI disturbances are reviewed in the next section. This section provides some of the criteria for the use of asbestos exposure data in a scientifically reliable risk assessment.

1. The appropriate measurement of exposure is the concentration of airborne fibers. Little information about risk can be obtained from dust measurements or measurements of the asbestos content of VAI.

   The EPA cancer risk factor is based on the inhalation exposure to airborne asbestos or asbestiform fibers, as is the OSHA PEL. Therefore, airborne asbestos fiber exposure is the appropriate measure for exposure assessment. Sometimes dust measurements, including a percentage or quantification of the dust that is asbestos, are reported. Dust measurements may be useful for determining the presence of asbestos, but are not relevant for quantitative risk assessment. Additionally, measurements of the asbestos content of VAI may also be made. These measurements are useful for determining the presence of asbestos, but are not useful for estimating risks. Also, the presence of certain minerals (e.g., tremolite) in VAI does not necessarily mean that asbestos is available to become airborne. The VAI must be disturbed before any asbestos becomes airborne. Even during disturbance of VAI, not all asbestos will become airborne. Only those particles of respirable size dimensions are relevant to a proper risk assessment.

2. For a proper comparison with the EPA cancer risk factor, exposure measurements must be collected using Transmission Electron Microscopy (TEM) and converted to an equivalent value for Phase Contrast Microscopy (PCM), or a PCM-equivalent (PCME).

   There are two microscopic techniques that are commonly used for measuring asbestos fibers that are collected in air. TEM is the most sensitive measurement technology; it can detect the widest size range of fibers and can differentiate between asbestos and non-asbestos fibers. The older and less sensitive technique is PCM. The PCM method cannot distinguish between asbestos and non-asbestos fibers, and cannot detect as small a size of fibers compared to TEM.

   Historically, most exposure measurements from the epidemiologic studies that formed the basis of the EPA cancer risk factor were done using PCM. Therefore, the EPA risk factor is based on asbestos fiber counts using PCM, which may be smaller than TEM counts as a result of the lower sensitivity. For this reason, fiber counts from TEM measurements cannot be compared with the EPA risk factor without an adjustment. On the other hand, the PCM

measurements in the epidemiologic studies were made in environments with large amounts of asbestos; thus, the inability to differentiate asbestos and non-asbestos fibers did not significantly affect these fiber counts. By contrast, PCM measurements in non-occupational environments, such as a home, where other types of structures other than asbestos are present (e.g., in the airborne dust during a disturbance of vermiculite) may result in overestimates of fiber counts. Therefore, the appropriate exposure measure is with fiber counts from TEM, and converted to a PCME (or PCM-equivalent) by excluding fibers in the size range that could not be measured by PCM and with appropriate determination of which fibers are asbestos. Specifically, only TEM fibers greater than 0.4 microns (μm) in diameter and greater than 5 μm in length should be included in the PCME fiber counts.

This concept is outlined in EPA's IRIS file on asbestos, which states: "The unit risk is based on fiber counts made by phase contrast microscopy (PCM) and should not be applied directly to measurements made by other analytical techniques" (emphasis ours). Further, the IRIS file states: "It should be understood that while TEM can be specific for asbestos, PCM is a nonspecific technique and will measure any fibrous material. Measurements by PCM which are made in conditions where other types of fibers may be present may not be reliable." These statements have been interpreted to develop the PCME concept, and the EPA has routinely applied it in risk assessments.

3. The asbestos concentration can be overestimated if the indirect filter preparation technique is used. The direct preparation technique should be used for the most accurate results.

Sometimes filters collected in dusty environments can be overloaded if an improper sampling volume is collected. In these situations, some microscopists manipulate the filter, such as through sonication, to produce a suspension of particles in a transfer medium, which is then filtered onto a new filter for analysis. According to the expert report of Dr. Richard Lee, the indirect preparation of the filter can breakup asbestos bundles and clusters that were single structures in the air into numerous individual fibers (Lee, 2003). This manipulation results in an overestimate of the actual asbestos concentration in the air. In addition to their own analysis, Dr. Lee cites an EPA report which also found that the indirect transfer technique leads to higher fiber counts than the direct transfer technique (EPA, 1990b).

4. Many samples taken in an environment with asbestos may contain cleavage fragments. Cleavage fragments are not asbestiform material and are, at the least, not as toxic or carcinogenic as asbestiform fibers. Therefore, cleavage fragments must be considered separately in fiber counts for appropriate risk assessment.

   While certain amounts and sizes of asbestiform fibers are known to be carcinogenic, the same is not true of tremolite cleavage fragments, which also may appear in microscopic analyses of amphibole asbestos. As Dr. Ilgren has certified in his expert report, there are fundamental differences in the properties of cleavage fragments and asbestiform fibers that explain the observed differences in carcinogenic potential (Ilgren, 2003). Asbestos fibers generally exist as bundles of very long, thin fibers that display extreme strength, flexibility, durability, and acid resistance. Cleavage fragments do not have these properties. Cleavage fragments are formed when nonasbestiform amphibole is crushed and slivers of mineral randomly break off (or "cleave") from the parent material so that they may look like fibers. However, cleavage fragmentation does not yield significant quantities of long, thin fibers of the dimensions that contribute substantially to carcinogenic risk. Instead, cleavage fragments are brittle and weak, and lack strength, durability, and acid resistance. In stark contrast to asbestos fibers, cleavage fragments are not strongly biopersistent in the human body, which significantly limits the toxicological potential.

   Dr. Ilgren provides a review of the available animal toxicology and human epidemiologic data on cleavage fragments, and concludes that cleavage fragments are not carcinogenic. To the best of my knowledge, the claimants make no mention whatsoever of cleavage fragments in their reports and have failed to separate cleavage fragments from asbestiform fibers in their fiber counts. The lack of any consideration of cleavage fragments by the claimants represents a serious scientific deficiency in their reports.

   It is important to note that EPA has advised that cleavage fragments should not be included in fiber counts for comparison with its IRIS cancer risk factor (Lioy et al., 2002).

D. Risk characterization: *EPA and other regulatory authorities have established criteria for assessing the acceptability of risks, which can be applied to characterize the magnitude of the risk associated with VAI.*

After developing quantitative estimates of risk, or the probability of an individual getting a disease from an exposure, it is necessary to establish what risk is acceptable. It must be understood that we accept small risks in our everyday lives, from driving to work, to what we eat, or how we spend our recreational time. Regulatory authorities are concerned with risks that are considered unacceptable to citizens. The definition of an acceptable risk is a value judgment that takes into account many factors, including the uncertainty in the assessment, the costs of remedial action, and the magnitude of risks that are generally found to be acceptable to individuals. This report relies on ranges of acceptable risk established by the EPA, and used in EPA regulatory actions.

For carcinogens, EPA has set forth and supports an acceptable risk range of individual risk from cancer of 10^{-6} (one in a million) to 10^{-4} (one in ten thousand). For example, the National Contingency Plan (NCP) sets forth the procedures that must be followed by EPA and private parties in selecting and conducting Superfund response actions. The NCP defines the acceptable risk range as follows:

> "For known or suspected carcinogens, acceptable exposure levels are generally concentration levels that represent an excess upper bound lifetime cancer risk to an individual of between 10^{-4} and 10^{-6} using information on the relationship between dose and response."

EPA expanded on its definition of the acceptable risk range in 1991 in its document "The role of baseline risk assessment in Superfund remedy selection decisions" (EPA, 1991):

> "For sites where cumulative site risk to an individual based on reasonable maximum exposure for both current and future land use is less than 10^{-4}, action is generally not warranted, but may be warranted if a chemical specific standard that defines acceptable risk is violated or unless there are noncarcinogenic effects or an adverse environmental impact that warrants action."

The acceptable risk range has also been adopted by other programs within EPA, including the drinking water (Cotruvo and Vogt, 1990) and air (NRDC v. EPA, 1987) programs.